Novel Tetracyclic Imidazole Derivatives: Synthesis, Dynamic NMR Study, and Anti-Inflammatory Evaluation

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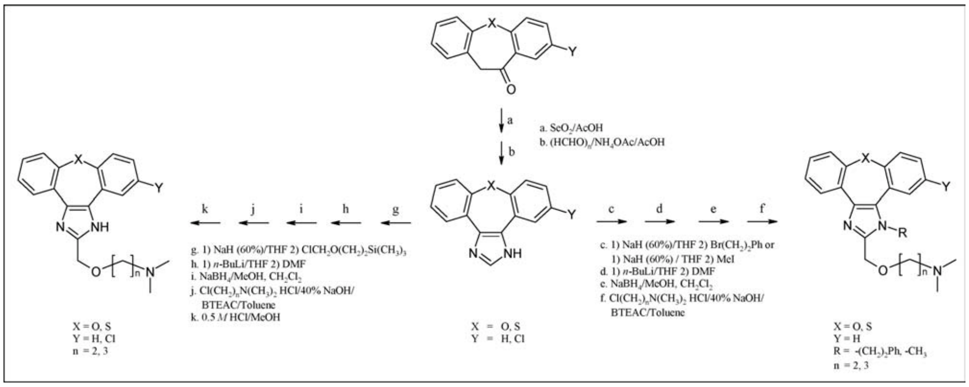

A series of tetracyclic imidazole derivatives **9a–9v** and **10a–10h** are prepared by multistep route starting from the known tricyclic diketones **2a–2d**. Intermediary dibenzooxepin[4,5-*d*]imidazoles (**3a**, **3c**) and dibenzothiepin[4,5-*d*]imidazoles (**3b**, **3d**) are *N*-protected to **4e, 4f** and to the isomeric compounds **5a**, **5b** and **6a**, **6b**. The isomeric compounds **5** and **6** are separated. Compounds **4**, **5,** and **6** are formylated at C(2) to afford **7a–7j**. In the last steps, aldehyde group is reduced, then alkylated to the two sets of isomeric ω-dimethylaminoalkyl derivatives **9a–9v**. *N*-deprotection of **9i–9v** led to the compounds **10a–10h**. Assignment of the *syn*/*anti* structure to **5a** and **6a** was supported by 1D selective ROESY NMR spectra, whereas conformational mobility for the selected representatives **8a** and **8b** is studied by dynamic NMR. Activation energies (energy barriers for interconversion) are determined to be ~11.5 and 16.2 kcal/mol, respectively. A series of derivatives **9** and **10** were tested *in vitro* for their anti-inflammatory activity.

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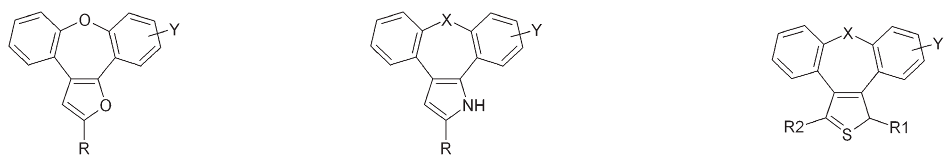
INTRODUCTION

In our continuing efforts toward the development of disease modifying treatments for rheumatoid arthritis (RA), we are targeting inhibition of overproduction of tumor necrosis factor alpha cytokine (TNF-α) that is recognized as a key cytokine in RA progression. A small molecule inhibitor of TNF-α would be a novel potent anti-inflammatory drug having this distinguished mechanism of action. In the frame of our project aimed toward synthesis, structure determination of tetracyclic imidazoles, and screening of their activity on the selected biological targets, we entered the study of a large series of dibenzo-oxepin- and dibenzo-thiepin imidazole derivatives. In our previous articles we have reported on the synthesis, properties, and preliminary biological results of oxa-, aza-, and thia-dibenzoazulenes, characterized by the annulated furane **I** [2], pyrrole **II**, **III** [3], and thiophene **IV**, **V** [4] ring (Fig. 1). Preliminary results have revealed activity of these polycyclic systems in the *in vitro* anti-inflammatory test in lipopolysaccharide (LPS) induced TNF-α production in human peripheral blood mononuclear cells (hPBMCs) that encouraged us to extend our effort on other five membered heterocyclic systems [5,6].

Generally, structural complexity of this specific class of recently studied non-steroidal anti-inflammatory compounds increases from diaryl-substituted heterocycles general formulae **VI**, to polycondensed heterocyclic structures **VII**. Representatives of the former are vicinaly substituted polycyclic aryl/pyridine-4-yls, potent inhibitors of p38 MAP kinase (p38) [7,8], while 2-substituted-4,5-diarylimidazoles **VIII** are claimed as *in vivo* anti-inflammatory active structures (Fig. 2) [9–14].

Moreover, polycondensed heterocycles with non-aromatic dibenzoazulene core and annelated 5-membered heterocycles are repeatedly claimed as anti-inflammatory active compounds. Among them are 2-substituted-1*H*-phenanthro[9,10-*d*]imidazoles **IX** [15], 2-substituted dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazoles **X** [16–20], 2-substituted dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazoles, and their corresponding sulfoxides and sulfones **XI** (Fig. 3) [21].

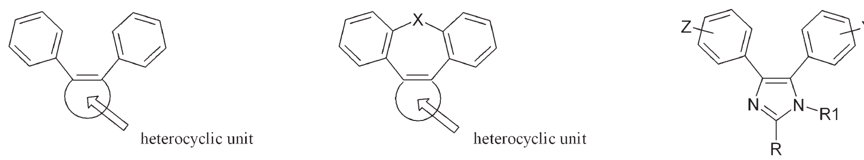


I Y = H, Cl, R = various substituents

II X = O, Y = H, Cl, R = various substituents
III X = S, Y = H, Cl, R = various substituents

IV X = O, Y = H, Cl, R1, R2 = various substituents
V X = S, Y = H, Cl, R1, R2 = various substituents

Figure 1. Previously described oxa-, aza-, and thia-dibenzoazulenes.

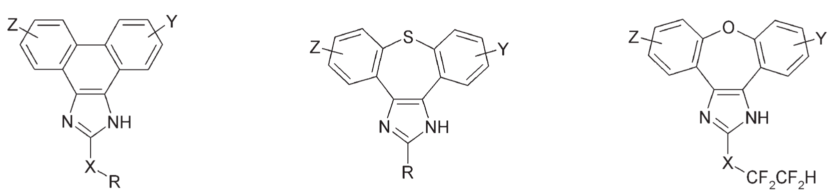


VI

VII X = O, S, CH_2

VIII Z, Y, R, R1 = various substituents

Figure 2. Non-steroidal heterocyclic anti-inflammatory compounds.



IX X = S, SO, SO_2,
Y, Z, R = various substituents

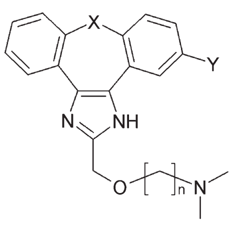
X Y, Z, R = various substituents

XI X = S, SO, SO_2,
Y, Z = various substituents

Figure 3. Polycondensed heterocycles with non-aromatic dibenzoazulene core.

Process for preparation of 2-formylimidazole acetals is also claimed [22], as well as 4,5-disubstituted imidazole derivatives and their use in CSBP/PK/p38 kinase mediated diseases [13]. First synthesis of tetracyclic, polycondensed imidazoles, presented by the formulae **X**, was reported by Lombardino [17], based on the general imidazole synthesis of Davidson *et al*. [23]. The same author claimed that a wide range of polycyclic compounds have anti-inflammatory and some other activities [16,18–20]. This method has been recently improved using microwave irradiation [24,25].

We have extended our effort to the imidazo-derivatives general formulae **XII**, wherein an extra basic unit was introduced at the imidazole ring to improve physicochemical properties of this series of compounds (Fig. 4).



XII X = O, S, Y = H, Cl
n = 2, 3

Figure 4. Novel tetracyclic imidazole derivatives.

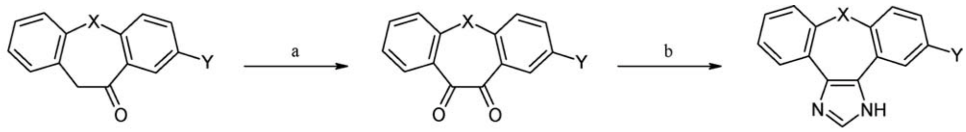
RESULTS AND DISCUSSION

Chemistry. Tetracyclic imidazoles **3a–3d** were prepared starting from the known 11*H*-dibenzo[*b,f*]oxepin-10-ones **1a**, **1c** or 11*H*-dibenzo[*b,f*]thiepin-10-ones **1b**, **1d**, cyclic ketones characterized by activated methylene group in the α-position to carbonyl group [16–20]. This group was oxidized by selenium dioxide to give α-diketones **2a–2d.** Synthesis of imidazoles **3a–3d** was completed by condensation of dicarbonyl compounds **2a–2d** with paraformaldehyde and ammonium acetate in acetic acid, according to Davidson *et al*., Scheme 1 [23].

N-Alkylated compounds **4a–4f** were obtained from **3a**, **3b** using a modified method by Wolkenberg *et al*. [25], on treatment with sodium hydride in tetrahydrofuran at 0°C followed by alkylation at elevated temperatures, Scheme 2 [26].

We have used 2-trimethylsilyl-ethoxymethyl (SEM) as effective protecting group for imidazole N(1) atom

Scheme 1



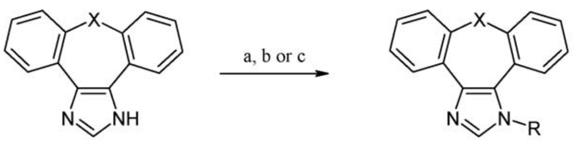
1a X = O, Y = H
1b X = S, Y = H
1c X = O, Y = Cl
1d X = S, Y = Cl

2a X = O, Y = H
2b X = S, Y = H
2c X = O, Y = Cl
2d X = S, Y = Cl

3a X = O, Y = H
3b X = S, Y = H
3c X = O, Y = Cl
3d X = S, Y = Cl

Reagents and conditions:
a. SeO_2/AcOH/reflux
b. $(HCHO)_n/NH_4OAc$/AcOH/reflux

Scheme 2



3a X = O
3b X = S

4a X = O, R = $-CH_3$
4b X = S, R = $-CH_3$
4c X = O, R = $-(CH_2)_2Ph$
4d X = S, R = $-(CH_2)_2Ph$
4e X = O, R = $-CH_2O(CH_2)_2Si(CH_3)_3$
4f X = S, R = $-CH_2O(CH_2)_2Si(CH_3)_3$

Reagents and conditions:
a. 1) NaH (60%)/THF/0 °C 2) $Br(CH_2)_2Ph$/reflux
b. 1) NaH (60%)/THF/0 °C 2) MeI/rt
c. 1) NaH (60%)/THF/0 °C 2) $ClCH_2O(CH_2)_2Si(CH_3)_3$/rt

which was introduced using (2-trimethylsilyl)-ethoxymethyl chloride (SEMCl) [27].

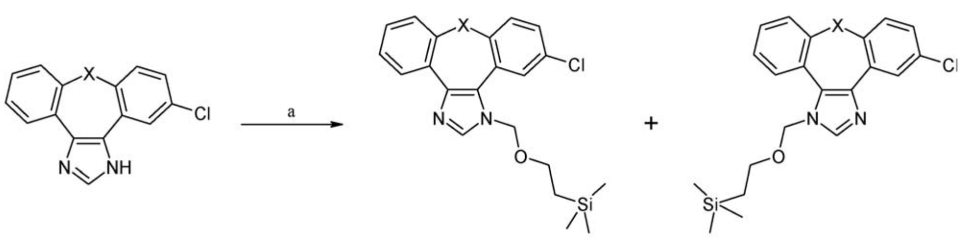
In the polycondensed imidazole derivatives **3a**, **3b** (Y = H) two tautomeric forms are equivalent and, therefore, single isomers **4a–4f** are obtained on alkylation. However, *N*(1)-alkylation of **3c**, **3d** affords structural isomers **5** and **6**, Scheme 3.

N-Trimethylsylil-ethoxymethylated compounds **5a**, **6a** and **5b**, **6b** were separated by purification on silica gel SPE cartridge using step gradient system for elution with ethyl acetate/*n*-hexane. In both cases, regioisomers **5a**, **6a** and **5b**, **6b** are obtained in ~1:1 ratio, revealing minor effect of electron-withdrawing chlorine in the *meta*-position of the aromatic ring. 1D NMR spectra of compounds in the isomeric series **5** and **6** did not give any clue on exact position of the side-chain on N(1) atom of imidazole. Straightforward determination required combined use of 2D NMR techniques and 1D selective ROESY spectrum, as exemplified for the compounds **5a** and **6a** (Fig. 5).

Correlation peaks from COSY, HMBC, HMQC, and 2D TPPI NOESY spectra afforded ambiguous information due to the overlap of key signals, so final solution for this problem came from the analysis of the selective 1D ROESY spectrum. Selective excitation was applied to methylenic protons of $N—CH_2—O$ unit at 5.356 and 5.372 ppm. NOE interactions were expected between methylenic protons of $N—CH_2—O$ group and *ortho*-protons in the vicinal aromatic ring, H_B for **5a** and H_A for **6a**, which are close enough to engage in dipolar interaction through space, (Fig. 6).

Protons H_A and H_B in both **5a** and **6a** have very close chemical shifts at the applied magnetic field, and are unequivocally assigned on the basis of their coupling patterns. Thus, H_A is coupled with *ortho*- and *meta*-proton giving dd at 7.84 ppm, whereas H_B is coupled only with *meta*-situated proton giving doublet at 7.86 ppm. On selective excitation of methylenic protons of $N—CH_2—O$ unit in **6a** doublet of H_B proton disappeared, while resonance lines for proton H_A remained, revealing its vicinity to the methylenic group, and thus *syn* (*cis*) orientation of the side chain on N(1) of imidazole ring to the aromatic ring that has no chlorine in *meta*-position to the annulated heterocycle.

Scheme 3



3c X = O
3d X = S

5a X = O
5b X = S

6a X = O
6b X = S

Reagents and conditions:
a. 1) NaH (60%)/THF/0 °C 2) $ClCH_2O(CH_2)_2Si(CH_3)_3$/rt

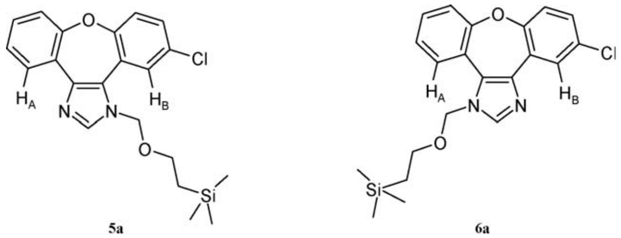


Figure 5. Regioisomeres determined by 2D NMR techniques and 1D selective ROESY spectrum.

Having this result in hands, ulterior synthetic steps have been performed on the separated isomers with known structure. From **4**, **5,** and **6** are obtained C(2) formylated derivatives **7** on generation of carbanion at C(2) of imidazole ring by *n*-butyllithium/tetrahydrofuran at −78°C, followed by treatment with DMF at r.t., Scheme 4 [9,28].

Reduction of **7a–7h** with sodium borohydride at r.t. afforded benzylic alcohols **8a–8h**. From **7i** and **7j** under the same conditions are obtained **8i** and **8j**. Both sets of hydroxymethyl imidazole derivatives are converted to dialkylaminoalkyl ethers **9a–9v** on treatment with ω-chloroalkyl-dimethylamines under phase transfer conditions in the presence of benzyltriethylammonium chloride (BTEAC), Scheme 5 [4,29].

Products **10a–10h** are obtained on cleavage of 2-(trimethylsilyl)ethoxymethyl group with 0.5*M* hydrochloric acid/methanol, Scheme 6 [9].

Conformational properties of representative oxepin (8a) and thiepin (8b) tetracycles. Conformational mobility and preferred conformation in solution of the 7-membered ring play an important role in biological activity of non-aromatic polycyclic compounds. Illustrative example represents octoclothepin **14** (Fig. 7), centrochiral, and planar-chiral compound with dibenzo-thiepine tricyclic core, wherein two conformers with inversed 7-membered ring are diastereotopic. An early study of (*S*)-**14** (Fig. 7), neuroleptic compound that binds on dopamine D-2 receptor [30], has revealed that stable conformation of (*S*)-**14**, which is responsible for the dopamine D-2 receptor antagonism, is significantly different from the one observed in the crystal [31].

On the other hand, conformational mobility of dibenzothiepines with sulfide **1b** and sulfoxide **15** unit in the bridge, was studied by dynamic NMR [32]. Huge difference in the activation energies for ring-inversion was observed; 9.3 kcal/mol for **1b** and 23 kcal/mol for **15**, revealing that at ambient temperature only the later may be separated into stable conformers (Fig. 8).

For many condensed non-aromatic heterocycles with one heteroatom in the 7-membered ring correlation between conformational properties and biological activities are studied. Detailed study of *N*-acylbenzazepines with interesting pharmacological properties [33], by dynamic NMR is an instructive case [34–36]. For dihydrobenz/*b*/azepines thermodynamic parameters for conformation equilibria are determined by dynamic NMR [37,38].

In view of the importance of conformational mobility of non-aromatic polycondensed heterocycles, we have determined difference in conformational mobility of the two representatives of oxepines and thiepines, compounds **8a** and **8b**, respectively. They are selected due

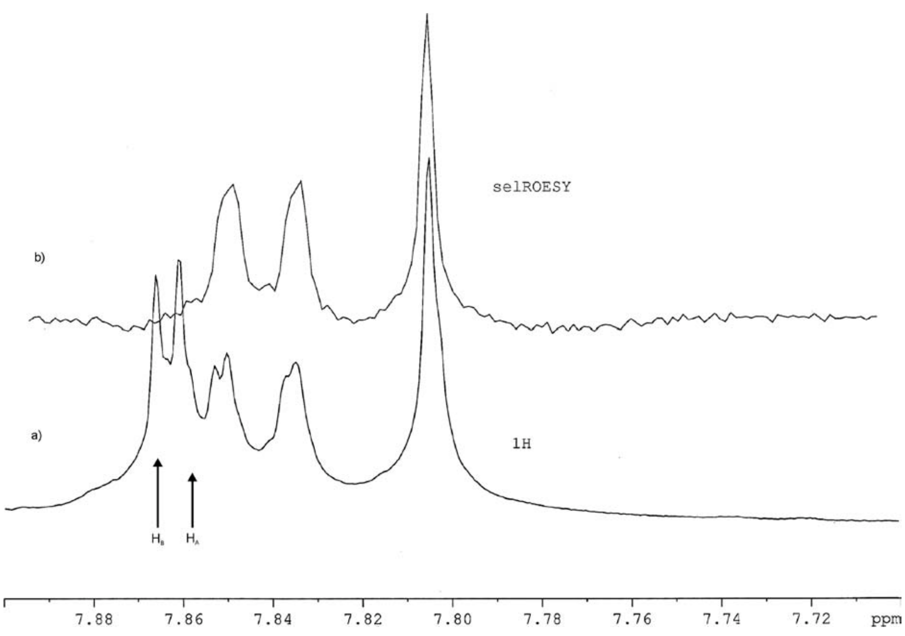
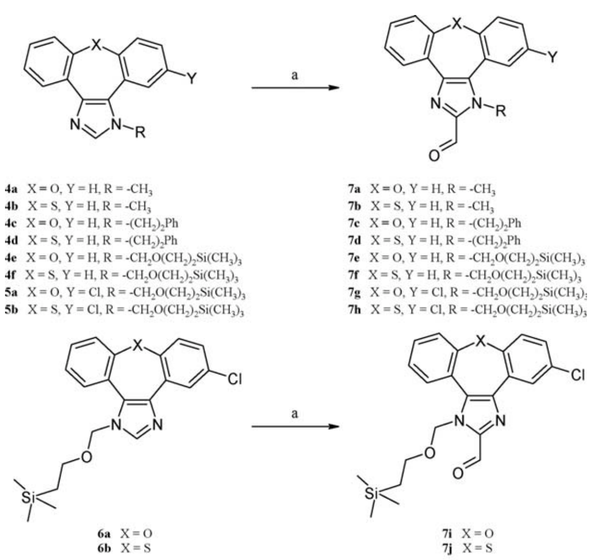


Figure 6. Comparison between aromatic region of ^1H (a) and 1D selective ROESY (b) spectra of **6a**.

Scheme 4



Reagents and conditions:
a. 1) *n*-BuLi/THF/-78 °C 2) DMF/rt

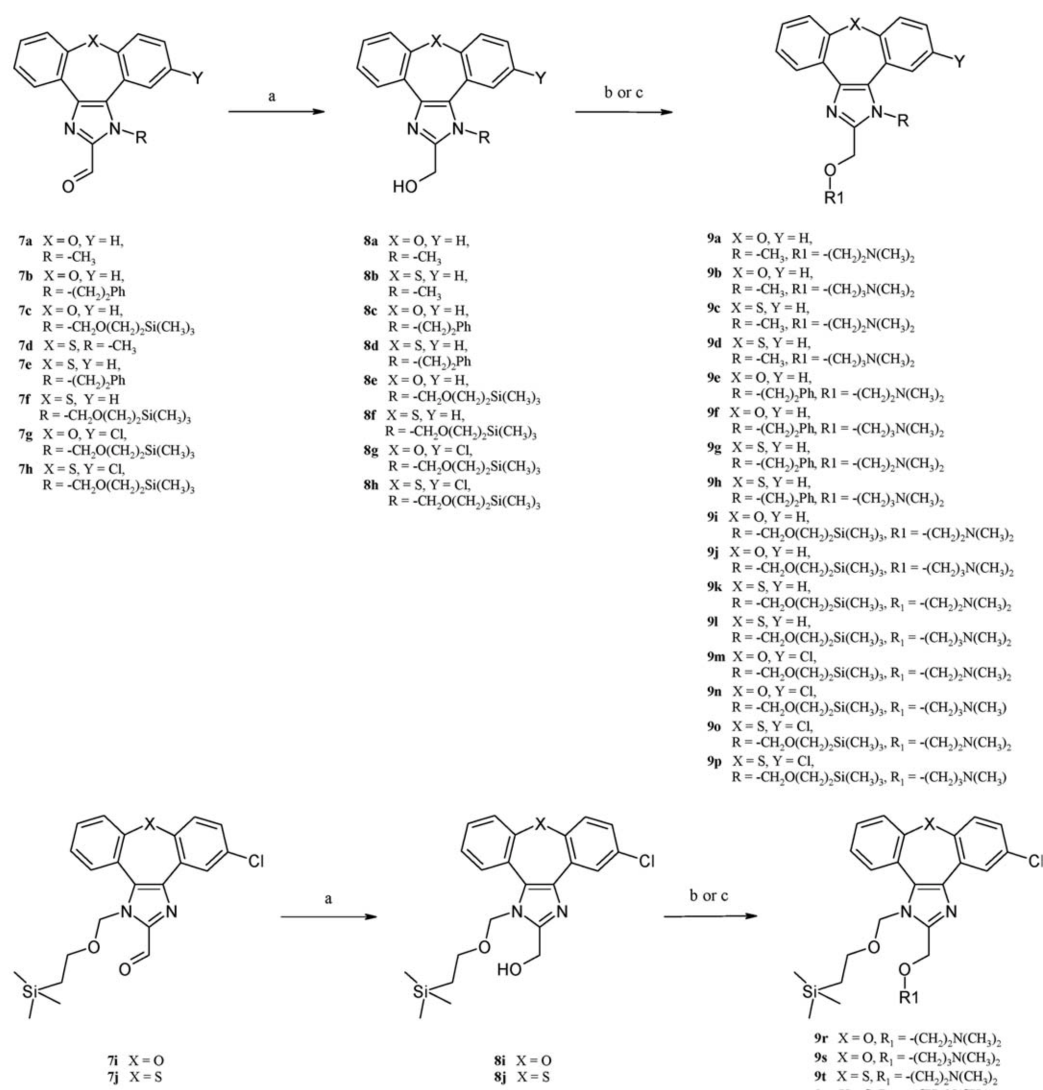
to their well resolved peaks for methylenic protons H_A, H_B, present in the 5-member chelate ring C(2)—CH_AH_B—O—H¨N(3) formed by hydrogen bond to N(3) atom, formulae **8a**, **8b** (Fig. 9).

On the basis of the reported results, we expected notable difference of the energy for conformational inversion for these two compounds. To our satisfaction, dynamic NMR study has revealed two different temperature intervals for the collapse of the AB(X) system into A_2 system of the methylenic protons. Series of proton NMR spectra acquired in temperature range where the coalescence of proton signals occurs are shown in the Figures 10 and 11.

Activation energies (energy barriers for interconversion) for compounds **8a** and **8b** are determined and results are presented in Table 1.

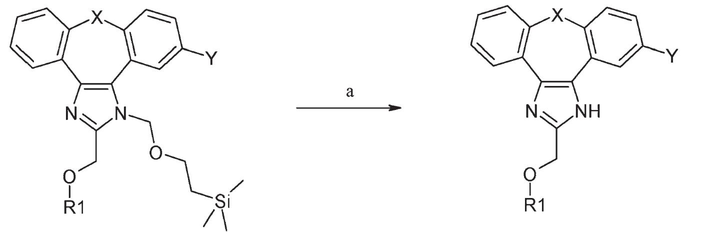
Biology. Among many discovered biological targets in the past 30 years, TNF-α, interleukin 1 (IL-1), p38, and COX-2 enzyme belong to the group of the most studied and the most relevant mediators of

Scheme 5



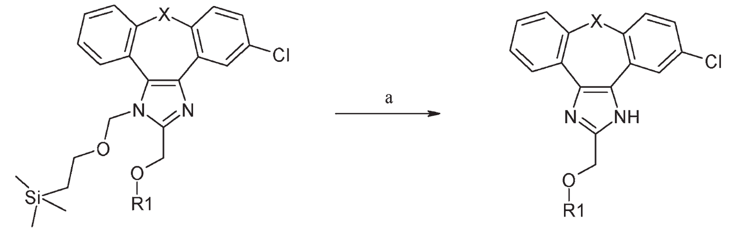
Reagents and conditions:
a. $NaBH_4$/MeOH, DCM/rt
b. $ClCH_2CH_2N(CH_3)_2$ HCl/40% NaOH/BTEAC/Toluene/109 °C
c. $ClCH_2CH_2CH_2N(CH_3)_2$ HCl/40% NaOH/BTEAC/Toluene/109 °C

Scheme 6



9i X = O, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
9j X = O, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
9k X = S, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
9l X = S, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
9m X = O, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
9n X = O, Y = Cl, R1 = -$(CH_2)_3N(CH_3)$
9o X = S, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
9p X = S, Y = Cl, R1 = -$(CH_2)_3N(CH_3)_2$

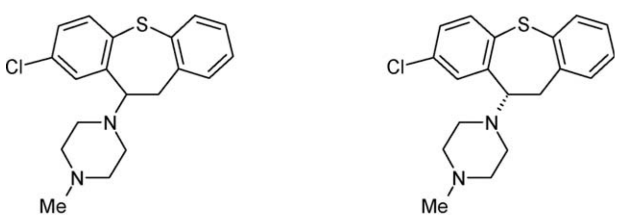
10a X = O, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
10b X = O, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
10c X = S, Y = H, R1 = -$(CH_2)_2N(CH_3)_2$
10d X = S, Y = H, R1 = -$(CH_2)_3N(CH_3)_2$
10e X = O, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
10f X = O, Y = Cl, R1 = -$(CH_2)_3N(CH_3)$
10g X = S, Y = Cl, R1 = -$(CH_2)_2N(CH_3)_2$
10h X = S, Y = Cl, R1 = -$(CH_2)_3N(CH_3)_2$



9r X = O, R_1 = -$(CH_2)_2N(CH_3)_2$
9s X = O, R_1 = -$(CH_2)_3N(CH_3)_2$
9t X = S, R_1 = -$(CH_2)_2N(CH_3)_2$
9v X = S, R_1 = -$(CH)_3N(CH_3)_2$

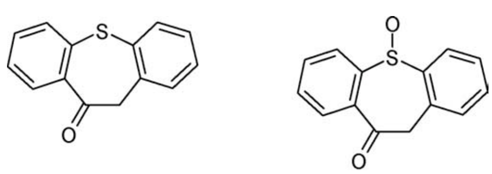
10e X = O, R1 = -$(CH_2)_2N(CH_3)_2$
10f X = O, R1 = -$(CH_2)_3N(CH_3)$
10g X = S, R1 = -$(CH_2)_2N(CH_3)_2$
10h X = S, R1 = -$(CH_2)_3N(CH_3)_2$

Reagents and conditions:
a. 0.5 *M* HCl in MeOH/MeOH/reflux



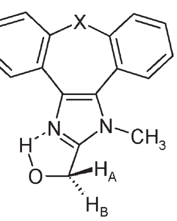
14 (*S*)-**14**

Figure 7. Octoclothepin and its (*S*)-conformer.



1b **15**

Figure 8. Dibenzothiepines with sulfide and sulfoxide unit in the bridge.



8a X = O
8b X = S

Figure 9. Methylenic protons H_A and H_B in the 5-membered chelate ring.

inflammation [39]. Overproduction inhibition of these cytokines which are responsible for inflammation has been proposed as a disease modifying approach towards the treatment of inflammatory disorders. The over-expression of TNF-α cytokine has been implicated in a number of serious inflammatory disorders. Consequently, agents that inhibit the production of TNF-α can decrease levels of inflammatory response, and thereby reduce inflammation and prevent further tissue destruction.

From medicinal chemistry point of view, connecting previous knowledge about anti-inflammatory properties of some compounds with today's understanding of important key players in inflammation mechanism could provide rational approach to the lead molecules that may be further optimized for better activity and

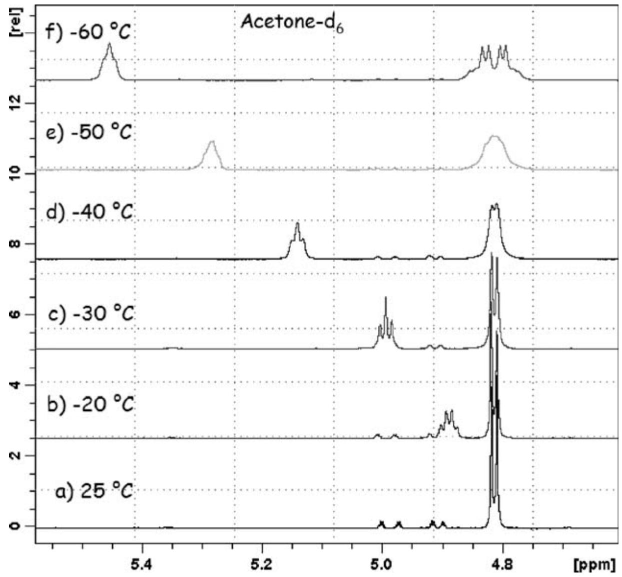


Figure 10. ^{1}H NMR spectra of **8a** acquired in acetone-d_6 in the temperature intervals from 25°C to −60°C (coalescence range for the H_A and H_B protons signals).

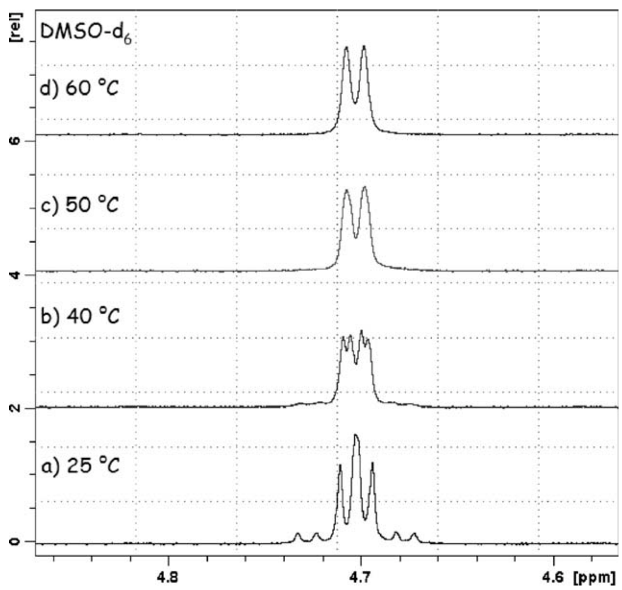


Figure 11. ^{1}H NMR spectra of **8b** acquired in DMSO-d_6 in the temperature intervals from 25°C to 60°C (coalescence range for the H_A and H_B protons signals).

selectivity profile and desirable pharmacokinetic properties. Along this line we have continued our project of the synthesis of tetracyclic target structures and their testing on inhibition of LPS stimulated TNF-α production. *In vitro* biological tests are performed on some intermediates and all tetracyclic compounds **9** and **10** to test their ability to inhibit TNF-α production in LPS-activated hPBMC assay [5,6].

Table 1

Activation energies for compounds **8a** and **8b**.

Compound	**8a**	**8b**
Solvent	Acetone-d_6	DMSO-d_6
Starting temperature (°C)	25	25
Ending temperature (°C)	−60	80
Coalescence temperature T_C (°C)	−40	50
Separation between signals Δν (Hz)	17.3	4.9
Coupling constant $^2J_{A,B}$ (Hz)	13.1	13.1
Rate constant at the coalescence temperature k_C (Hz)	80.9	72.1
Gibbs energy $\Delta G_C^{\ddagger}$ (kcal/mol)	11.5	16.2

‡ Activated complex, transition state.

Compounds possessing alkoxymethylene linker (ether) at position C(2) on imidazole ring showed potency to inhibit TNF-α production *in vitro* in low micromolar range with IC50 values for the most potent compounds in the range of 1–3 μ*M*.

According to obtained results dibenzo-oxepin- and dibenzo-thiepin imidazole derivatives were recognized as a novel class of tetracyclic compounds with anti-inflammatory activity through specific inhibition of TNF-α secretion.

EXPERIMENTAL

Chemistry. Commercial reagents were used as received without additional purification. All used chemicals and solvents were p.a. purity. Differential scanning calorimetry data were collected on a Mettler Toledo differential scanning calorimeter 822^e/500 using Mettler Toledo STAR^e software. Samples about 5 mg were weighed into Al-pans (40 μL) with pierced cover. Dry nitrogen was used as purge gas (purge: 50 mL/min). The heating rate of 10°C/min over the range 25–300°C was used. The instrument was calibrated using certified indium and zinc. IR spectra were recorded as potassium bromide (KBr) pastilles or as a film on a sodium chloride plate, on a Nicolet Magna IR 760 FT IR-spectrophotometer, and on a Bruker Vertex 70 as ATR (ZnSe) powder or film cast from DCM solution. One- and two-dimensional NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz), Bruker Avance DRX 500 (500 MHz), and Bruker Avance III 600 (600 MHz) spectrometers. Deuterated dimethylsulfoxide (DMSO-d_6) and deuterated chloroform ($CDCl_3$) were used as solvents and tetramethylsilan (TMS) as an internal standard. Purity of the compounds was obtained on a Waters HPLC-UV/MS Autopurification System with a Micromass ZQ and a Waters 996 Photodiode Array Detector, and on Varian Chrompack CP-3800 Gas Chromatograph with a Varian Chrompack Saturn 2000 MS/MS detector. HRMS data were acquired using Q-TOF 2 Waters system. Thin layer chromatography (TLC) was run on Merck Silica gel 60 F_{254} plates, spots detected with UV light at 254 and/or 365 nm. Proportions of solvents used for TLC are by volume.

Products were purified using Solid Phase Extraction (SPE) columns on an automated SPE purification system (FlashMaster II).

General procedure for reaction of ketones 1 with selenium dioxide (preparation of compounds 2). To the suspension of selenium dioxide (1.74 g, 15.70 mmol) in glacial acetic acid (10 mL) was added a solution of ketone **1** (14.3 mmol) in glacial acetic acid (30 mL). The suspension was heated for 2 h at 100°C and undissolved material filtered off. The filtrate was diluted with water (50 mL) and extracted with dichloromethane (2 × 50 mL). Organic extracts were washed with water (3 × 50 mL), and saturated sodium hydrogencarbonate (3 × 50 mL), dried over anhydrous sodium sulfate, concentrated, and then precipitated from *n*-hexane/dichloromethane to give compound **2**.

Dibenzo[*b,f*]oxepin-10,11-dione (2a). Obtained from **1a** as a yellow solid: Yield 85%; mp 116.68°C; IR (KBr): 1670, 1600, 1469, 1447, 1281, 1220, 926, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (td, *J* = 7.55, 1.07 Hz, 2H), 7.42–7.43 (m, 1H), 7.43–7.45 (m, 1H), 7.64–7.68 (m, 2H), 7.99 (d, *J* = 1.83 Hz, 1H), 8.00 ppm (d, *J* = 1.83 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 121.60, 125.50, 126.11, 131.71, 135.83, 156.65, 186.31 ppm; MS: *m/z* 225.00 $[M+H]^+$.

Dibenzo[*b,f*]thiepin-10,11-dione (2b). Obtained from **1b** as a yellow solid: Yield 80%; mp 122.69°C; IR (KBr): 1675, 1581, 1435, 1280, 1258, 1219, 916, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.37 (m, 4H), 7.51 (dd, *J* = 7.63, 1.53 Hz, 2H), 7.69 ppm (dd, *J* = 7.17, 1.98 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.23, 131.26, 132.09, 132.98, 134.55, 139.35, 190.62 ppm; MS: *m/z* 240.09 $[M+H]^+$.

2-Chlorodibenzo[*b,f*]oxepin-10,11-dione (2c). Obtained from **1c** as a yellow solid: Yield 74%; mp 103.23°C; IR (KBr): 1691, 1673, 1599, 1467, 1449, 1402, 1290, 1266, 1224, 1118, 842, 765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.44 (m, 3H), 7.60 (dd, *J* = 8.70, 2.59 Hz, 1H), 7.65–7.70 (m, 1H), 7.95–8.01 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.42, 136.01, 135.74, 131.87, 131.10, 130.89, 125.87, 123.36, 121.52 ppm; MS: *m/z* 259.1 $[M+H]^+$.

2-Chlorodibenzo[*b,f*]thiepin-10,11-dione (2d). Obtained from **1d** as a yellow solid: Yield 79%; mp 167.94°C; IR (KBr): 1689, 1583, 1274, 1213, 1094, 829, 761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.52 (m, 3H), 7.56–7.65 (m, 2H), 7.77 (d, *J* = 2.14 Hz, 1H), 7.80 ppm (dd, *J* = 7.02, 1.83 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 129.78, 131.25, 131.65, 132.44, 133.08, 133.21, 133.41, 133.73, 134.21, 135.92, 139.49, 140.76, 189.21, 189.83 ppm; MS: *m/z* 275.0 $[M+H]^+$.

General procedure for reaction of diketones 2 with paraformaldehyde (preparation of compounds 3). A suspension of compound **2** (5.35 mmol), ammonium acetate (4.13 g, 53.5 mmol), and paraformaldehyde (0.19 g, 5.0 mmol) in glacial acetic acid (32 mL) was heated to reflux. After 2 h, reaction mixture was cooled, diluted with water (100 mL), and extracted with ethyl acetate (2 × 50 mL). Organic extracts were washed with water (3 × 100 mL), saturated sodium hydrogencarbonate (3 × 100 mL), and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and then purified on silica gel SPE cartridge using step gradient system for elution dichloromethane/(dichloromethane/methanol/ammonium hydroxide 90:9:1.5) to give compound **3**.

1*H*-Dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (3a). Obtained from **2a** as a white solid: Yield 81%; mp 234.05°C; IR (KBr): 3286, 2941, 2871, 1730, 1165, 1096, 856 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.27 (d, *J* = 4.88 Hz, 2H), 7.32 (br. s., 2H), 7.37 (br. s., 2H), 7.55 (d, *J* = 7.02 Hz, 1H), 7.76 (d, *J* = 6.71 Hz, 1H), 7.96 (s, 1H), 12.92 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 121.48, 122.63, 126.44, 127.08, 127.36, 132.06, 136.66, 155.30 ppm; HRMS: *m/z* calcd. for $C_{15}H_{11}N_2O$: 235.0871 $[M+H]^+$, found 235.0865.

1*H*-Dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (3b). Obtained from **2b** as a yellow solid: Yield 75%; mp 263.23°C; IR (KBr): 2815, 2641, 1511, 1478, 953, 758, 651 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.37 (t, *J* = 7.17 Hz, 2H), 7.44 (t, *J* = 7.32 Hz, 2H), 7.59 (br. s., 3H), 7.81 (br. s., 1H), 7.99 (s, 1H), 12.92 ppm (br. s., 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 136.85, 133.60, 132.60, 132.17, 131.63, 130.90, 128.75, 128.35, 127.65, 126.85 ppm; HRMS: *m/z* calcd. for $C_{15}H_{11}N_2S$: 251.0638 [M+H]+, found 251.0630.

11-Chloro-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (3c). Obtained from **2c** as a beige amorphous solid: Yield 84%; IR (KBr): 3113, 14785, 953, 758, 651 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.29 (dt, *J* = 7.76, 3.97 Hz, 1H), 7.33–7.45 (m, 4H), 7.66 (br. s., 2H), 8.00 (s, 1H), 13.00 ppm (br. s., 1H), ^{13}C NMR (151 MHz, DMSO-d_6): δ 153.81, 152.60, 137.92, 129.36, 125.58, 123.37 ppm; HRMS: *m/z* calcd. for $C_{15}H_{10}ClN_2O$: 269.0482 $[M+H]^+$, found 269.0468.

11-Chloro-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (3d). Obtained from **2d** as a yellow solid: Yield 68%; mp 241.28°C; IR (KBr): 2806, 2639, 1475, 768, 649 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.33–7.53 (m, 3H), 7.53–7.67 (m, 3H), 7.78 (br. s., 1H), 8.04 (s, 1H), 13.03 ppm (d, *J* = 13.73 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 127.23, 127.48, 128.26, 129.55, 129.72, 130.00, 130.85, 131.02, 133.23, 133.31, 133.79, 133.97, 135.90, 137.76, 138.30 ppm; HRMS: *m/z* calcd. for $C_{15}H_{10}ClN_2S$: 285.0253 $[M+H]^+$, found 285.0245.

General procedures for *N*-alkylation of the compounds 3 (preparation of compounds 4). ***N-Methylation.*** To a solution of **3** (0.5 g, 2.13 mmol) in dry tetrahydrofuran (23 mL) the 60% suspension of NaH in mineral oil (0.26 g, 6.4 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then MeI (0.13 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (100 mL), and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution dichloromethane/(dichloromethane/methanol/ammonium hydroxide 90:5:0.5) *N*-methylated compounds **4a** and **4b** were isolated.

1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4a). Obtained from **3a** as a yellowish solid: Yield 73%; mp 138.05°C; IR (KBr): 1514, 1444, 1248, 1201, 810, 765, 733 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.91 (s, 3H), 7.26 (ddd, *J* = 7.55, 6.49, 2.14 Hz, 1H), 7.29–7.38 (m, 3H), 7.39–7.44 (m, 1H), 7.45–7.48 (m, 1H), 7.66 (dd, *J* = 7.63, 1.53 Hz, 1H), 7.71–7.74 (m, 1H), 7.94 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 33.62, 121.47, 122.63, 123.27, 125.78, 125.85, 126.65, 126.72, 126.83, 128.20, 129.20, 129.65, 137.54, 141.60, 155.79, 155.89 ppm; HRMS: *m/z* calcd. for $C_{16}H_{13}N_2O$: 249.1028 $[M+H]^+$, found 249.1019.

1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (4b). Obtained from **3b** as a yellowish solid: Yield 94%; mp 137.12°C; IR (KBr): 3051, 2922, 1510, 1467, 773, 758, 741, 643 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.83 (s, 3H), 7.33–7.37 (m, 1H), 7.40–7.50 (m, 3H), 7.57 (dd, J = 7.63, 1.22 Hz, 1H), 7.64 (dd, J = 7.63, 1.22 Hz, 1H), 7.70 (dd, J = 7.48, 1.37 Hz, 1H), 7.78 (dd, J = 7.63, 1.22 Hz, 1H), 7.97 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 33.49, 128.23, 128.37, 128.78, 129.15, 129.26, 130.57, 132.50, 133.16, 133.84, 134.16, 138.41, 140.73, 141.29 ppm; HRMS: m/z calcd. for $C_{16}H_{13}N_2S$: 265.0799 [M+H]$^+$, found 265.0791.

N-*Phenylethylation.* To a solution of **3** (0.2 g, 0.85 mmol) in dry tetrahydrofuran (7 mL) the 60% suspension of sodium hydride in mineral oil (0.10 g, 2.56 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-phenylethyl bromide (0.17 mL, 1.28 mmol) was added and reaction mixture was heated under stirring and reflux. After 2 h, another portion of the 60% suspension of sodium hydride in mineral oil (0.03 g, 0.85 mmol) and 2-phenylethyl bromide (0.12 mL, 0.85 mmol) were added and stirring under reflux was continued. After 1 day, another portion of the 60% suspension of sodium hydride in mineral oil (0.03 g, 0.85 mmol) and 2-phenylethyl bromide (0.12 mL, 0.85 mmol) were added and stirring under reflux was continued for 1 day. Then it was cooled to room temperature, concentrated, and diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution *n*-hexane/ethyl acetate *N*-phenylethylated compounds **4c** and **4d** were isolated.

1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4c). Obtained from **3a** as a yellowish amorphous solid: Yield 64%; IR (KBr): 1509, 1443, 1201, 1079, 809, 762, 741, 696 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.02 (t, J = 7.48 Hz, 2H), 4.55 (t, J = 7.48 Hz, 2H), 7.13–7.17 (m, 2H), 7.17–7.22 (m, 1H), 7.23–7.28 (m, 3H), 7.30–7.39 (m, 3H), 7.40–7.45 (m, 1H), 7.46–7.49 (m, 1H), 7.64–7.72 (m, 2H), 7.89 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.10, 47.44, 121.43, 122.69, 123.49, 125.75, 126.02, 126.07, 126.31, 126.82, 126.95, 128.13, 128.80, 128.99, 129.26, 129.72, 137.93, 138.02, 141.15, 155.81, 156.10 ppm; HRMS: m/z calcd. for $C_{23}H_{19}N_2O$: 339.1497 [M+H]$^+$, found 339.1496.

1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (4d). Obtained from **3b** as a white solid: Yield 79%; mp 156.93°C; IR (KBr): 3049, 3022, 2939, 1505, 756, 740, 658 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.79–2.95 (m, 2H), 4.36–4.45 (m, 1H), 4.58 (ddd, J = 13.73, 7.78, 5.34 Hz, 1H), 7.05–7.09 (m, 2H), 7.14–7.24 (m, 3H), 7.32–7.37 (m, 1H), 7.39–7.45 (m, 2H), 7.48 (td, J = 7.55, 1.37 Hz, 1H), 7.58 (dd, J = 7.63, 1.22 Hz, 1H), 7.64 (dd, J = 7.63, 1.53 Hz, 1H), 7.71 (dd, J = 7.63, 1.53 Hz, 1H), 7.75 (dd, J = 7.93, 1.53 Hz, 1H), 7.85 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.15, 47.36, 126.86, 127.97, 128.30, 128.73, 128.78, 128.99, 129.13, 129.31, 129.84, 132.50, 132.84, 133.59, 133.87, 134.39, 137.96, 138.32, 140.28, 141.84 ppm; HRMS: m/z calcd. for $C_{23}H_{19}N_2S$: 355.1269 [M+H]$^+$, found 355.1273.

N-*Trimethylsylil-ethoxymethylation.* To a solution of **3** (0.5 g, 2.13 mmol) in dry tetrahydrofuran (23 mL) the 60% suspension of sodium hydride in mineral oil (0.26 g, 6.40 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-(trimethylsilyl)ethoxymethyl chloride (0.38 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (100 mL), and extracted with dichloromethane (3 × 50 mL). The organic extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution ethyl acetate/*n*-hexane *N*-trimethylsylil-ethoxymethylated compounds **4e** and **4f** were isolated.

1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (4e). Obtained from **3a** as a yellowish solid: Yield 60%; mp 98.50°C; IR (KBr): 1513, 1250, 1244, 1080, 838, 766 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.93–0.98 (m, 2H), 3.68–3.73 (m, 2H), 5.57 (s, 2H), 7.29–7.36 (m, 2H), 7.39–7.42 (m, 2H), 7.44–7.52 (m, 2H), 7.78 (ddd, J = 7.48, 1.22, 1.07 Hz, 1H), 7.91 (dd, J = 7.93, 1.53 Hz, 1H), 8.22 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.03, 17.58, 65.96, 74.46, 121.50, 122.66, 123.16, 125.83, 125.98, 126.76, 126.94, 127.14, 127.92, 129.52, 130.04, 137.99, 141.99, 156.01, 156.09 ppm; HRMS: m/z calcd. for $C_{21}H_{25}N_2O_2Si$: 365.1685 [M+H]$^+$, found 365.1660.

1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]-thiepino[4,5-*d*]imidazole (4f). Obtained from **3b** as a yellowish solid: Yield 79%; mp 104.47°C; IR (KBr): 2955, 1504, 1248, 1083, 863, 835, 776, 763 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.85–0.97 (m, 2H), 3.55 (td, J = 9.54, 6.56 Hz, 1H), 3.69 (td, J = 9.46, 6.71 Hz, 1H), 5.46 (d, J = 11.29 Hz, 1H), 5.66 (d, 1H), 7.41–7.46 (m, 1H), 7.47–7.55 (m, 3H), 7.64 (dd, J = 7.63, 1.22 Hz, 1H), 7.75–7.79 (m, 1H), 7.85 (dd, J = 7.93, 1.22 Hz, 2H), 8.27 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.61, 66.02, 74.52, 128.46, 128.70, 129.06, 129.20, 129.27, 129.61, 130.49, 132.51, 132.61, 133.45, 133.90, 134.50, 138.08, 141.16, 141.69 ppm; HRMS: m/z calcd. for $C_{21}H_{25}N_2OSSi$: 381.1451 [M+H]$^+$, found 381.1436.

General procedure for *N*-trimethylsylil-ethoxymethylation of the compounds 3 (preparation of structural isomers 5 and 6). To a solution of **3** (1.0 g, 3.72 mmol) in dry tetrahydrofuran (30 mL) the 60% suspension of sodium hydride in mineral oil (0.45 g, 11.20 mmol) was added under stirring at 0°C. The reaction mixture was stirred for 30 min at 0°C, then 2-(trimethylsilyl)ethoxymethyl chloride (0.66 mL, 3.72 mmol) was added and reaction mixture was stirred at room temperature for 2 h. Then it was concentrated, diluted with water (30 mL), and extracted with dichloromethane (3 × 25 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution ethyl acetate/*n*-hexane structural isomers **5** and **6** were isolated.

11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (5a). Obtained from **3c** as a yellowish solid: Yield 31%; mp 84.67°C; IR (KBr): 3093, 2957, 1515, 1245, 1200, 1077, 833, 768 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.96 (t, J = 7.9 Hz, 2H), 3.72 (t, J = 8.0 Hz, 2H), 5.56 (s, 2H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H), 7.77 (d, J = 7.0 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 8.25 ppm (s, 1H) ^{13}C NMR (126 MHz, DMSO-d_6): δ−1.04, 17.58, 66.04, 74.55, 122.69, 122.80, 123.46, 126.04, 126.28, 127.27, 127.47, 129.07, 129.74, 129.94, 130.37, 136.67, 142.32, 154.50, 155.78 ppm ; HRMS: m/z calcd. for $C_{21}H_{24}N_2O_2SiCl$: 399.1296 [M+H]$^+$, found 399.1281.

11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (5b). Obtained from **3d** as a yellowish solid: Yield 33%; mp 117.74°C; IR (KBr): 2976, 2940, 1738, 1621, 1456, 1381, 1169, 1074, 1014, 732 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 0.00 (m, 9H), 0.932 (m, 2H), 3.60 (td, J = 9.7, 6.4 Hz, 1H), 3.71 (td, J = 9.7, 6.5 Hz, 1H), 5.41 (d, J = 11.3 Hz, 1H), 5.63 (d, J = 11.3 Hz, 1H), 7.43 (ddd, J = 7.6, 7.5, 1.5 Hz, 1H), 7.50 (td, J = 7.5, 1.3 Hz, 1H), 7.53 (dd, J = 8.3, 2.4 Hz, 1H), 7.62 (dd, J = 7.8, 1.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 7.7, 1.2 Hz, 1H), 7.95 (d, J = 2.3 Hz, 1H), 8.28 ppm (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6): δ −0.01, 18.67, 67.04, 75.52, 129.00, 129.61, 130.20, 130.28, 130.38, 130.43, 133.55, 134.00, 134.08, 135.18, 135.36, 136.37, 138.88, 142.55, 143.45 ppm ; HRMS: m/z calcd. for $C_{21}H_{24}N_2OSClSi$: 415.1067 $[M+H]^+$, found 415.1067.

5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole (6a). Obtained from **3c** as a yellowish solid: Yield 47%; mp 93.25°C; IR (KBr): 2950, 1514, 1246, 1094, 1074, 834, 811 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.00 (m, 9H), 0.96 (t, J = 7.9 Hz, 2H), 3.72 (t, J = 8.0 Hz, 2H), 5.56 (s, 2H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H), 7.77 (d, J = 7.0 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 8.25 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −0.98, 17.57, 66.03, 74.42, 121.50, 124.37, 124.95, 125.53, 126.11, 126.45, 127.06, 127.56, 129.53, 129.86, 130.17, 138.80, 142.44, 154.55, 155.76 ppm ; HRMS: m/z calcd. for $C_{21}H_{24}N_2O_2SiCl$: 399.1296 $[M+H]^+$, found 399.1289.

5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole (6b). Obtained from **3d** as a yellowish solid: Yield 49%; mp 113.80°C; IR (KBr): 3098, 2950, 1583, 1505, 1407, 1330, 1263, 1249, 1091, 1083, 1071, 1019, 859, 838, 810, 767, 638 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.91 (m, 2H), 3.55 (td, J = 9.6, 6.7 Hz, 1H), 3.69 (td, J = 9.5, 6.8 Hz, 1H), 5.48 (d, J = 11.3 Hz, 1H), 5.67 (d, J = 11.3 Hz, 1H), 7.50 (dd, J = 8.4, 2.4 Hz, 1H), 7.53 (m, 1H), 7.55 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.77 (m, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.87 (m, 1H), 8.31 ppm (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 0.00, 18.67, 67.16, 75.69, 128.73, 129.81, 129.88, 130.62, 130.99, 132.24, 133.21, 133.45, 134.96, 135.04, 135.08, 135.22, 140.88, 141.49, 142.55 ppm; HRMS: m/z calcd. for $C_{21}H_{24}N_2OSClSi$: 415.1067 $[M+H]^+$, found 415.1053.

General procedure for C(2) formylation of the compounds 4, 5, and 6 (preparation of compounds 7). To a solution of **4** (0.44 g, 1.77 mmol) in dry tetrahydrofuran (8 mL) 1.6*M* solution of *n*-butyllithium in *n*-hexane (1.22 mL, 1.95 mmol) was added under stirring at −78°C. The reaction mixture was stirred for 15 min at −78°C, then dry DMF (0.17 mL, 2.13 mmol) was added and reaction mixture was stirred at room temperature for 1 h. Then it was diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with brine (50 mL), dried over anhydrous sodium sulfate, evaporated, and then purified on silica gel SPE cartridge using step gradient system for elution *n*-hexane/dichloromethane to give compound **7**.

1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole-2-carbaldehyde (7a). Obtained from **4a** as a yellow solid: Yield 74%; mp 161.69°C; IR (ATR): 2921, 2849, 1681, 1511, 1445, 1209, 800, 768, 745 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.17 (s, 3H), 7.31–7.41 (m, 2H), 7.44–7.46 (m, 2H), 7.55–7.57 (m, 2H), 7.74–7.80 (m, 1H), 7.83 (d, J = 7.63 Hz, 1H), 9.88 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 34.48, 121.44, 121.73, 122.96, 126.13, 126.21, 126.75, 127.16, 128.33, 130.46, 131.64, 133.19, 139.34, 144.74, 156.88, 157.26, 182.69 ppm; HRMS: m/z calcd. for $C_{17}H_{13}N_2O_2$: 277.0977 $[M+H]^+$, found 277.0963.

1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole-2-carbaldehyde (7b). Obtained from **4b** as a yellow solid: Yield 52%; mp 215.10°C; IR (ATR): 2918, 2835, 1682, 1443, 825, 760 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 4.08 (s, 3H), 7.41–7.52 (m, 2H), 7.52–7.57 (m, 2H), 7.65 (dd, J = 7.78, 1.37 Hz, 1H), 7.71–7.80 (m, 2H), 7.87 (dd, J = 7.78, 1.68 Hz, 1H), 9.92 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 34.46, 128.63, 129.39, 129.58, 129.72, 129.85, 130.80, 130.89, 132.78, 134.26, 134.30, 135.74, 136.40, 137.03, 142.85, 143.76, 182.99 ppm; HRMS: m/z calcd. for $C_{17}H_{13}N_2OS$: 293.0749 $[M+H]^+$, found 293.0740.

1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole-2-carbaldehyde (7c). Obtained from **4c** as a yellowish solid: Yield 70%; mp 157.69°C; IR (ATR): 3062, 3025, 2821, 1674, 1508, 1449, 1421, 1202, 770, 743 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 3.03 (t, J = 7.32 Hz, 2H), 4.90 (t, J = 7.48 Hz, 2H), 7.07–7.11 (m, 2H), 7.15–7.24 (m, 3H), 7.33 (ddd, J = 7.55, 6.03, 2.59 Hz, 1H), 7.38–7.49 (m, 3H), 7.49–7.57 (m, 2H), 7.75–7.82 (m, 2H), 9.82 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.41, 47.23, 121.64, 123.02, 126.17, 126.31, 126.72, 127.06, 127.29, 127.72, 128.79, 128.88, 130.51, 131.65, 132.70, 137.41, 139.83, 144.54, 157.18, 157.57 ppm, 182.55; HRMS: m/z calcd. for $C_{24}H_{19}N_2O_2$: 367.1447 $[M+H]^+$, found 367.1454.

1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole-2-carbaldehyde (7d). Obtained from **4d** as a yellowish solid: Yield 52%; mp 193.04°C; IR (ATR): 1684, 1421, 827, 748, 696 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.80–2.95 (m, 2H), 4.74 (dt, J = 14.04, 7.02 Hz, 1H), 5.04 (dt, J = 14.11, 7.13 Hz, 1H), 6.95–6.99 (m, 2H), 7.12–7.17 (m, 3H), 7.42 (td, J = 7.55, 1.68 Hz, 1H), 7.46–7.57 (m, 3H), 7.62 (dd, J = 7.63, 1.22 Hz, 1H), 7.72–7.77 (m, 2H), 7.83 (dd, J = 7.48, 1.68 Hz, 1H), 9.81 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.48, 46.88, 126.91, 128.68, 128.72, 128.89, 129.29, 129.51, 129.71, 130.69, 131.12, 132.71, 132.77, 134.26, 134.90, 136.03, 136.38, 136.97, 137.30, 143.46, 182.82 ppm; HRMS: m/z calcd. for $C_{24}H_{19}N_2OS$: 383.1218 $[M+H]^+$, found 383.1229.

1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole-2-carbaldehyde (7e). Obtained from **4e** as a white solid: Yield 78%; mp 83.24°C; IR (ATR): 952, 1686, 1507, 1450, 1430, 1240, 1211, 1082, 856, 832, 801, 762, 691 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.93–0.98 (m, 2H), 3.73–3.79 (m, 2H), 5.93 (s, 2H), 7.36–7.46 (m, 2H), 7.49–7.57 (m, 2H), 7.57–7.65 (m, 2H), 7.87–7.96 (m, 1H), 7.96–8.04 (m, 1H), 9.97 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.71, 66.45, 73.60, 121.51, 121.71, 123.04, 126.26, 126.35, 126.51, 127.35, 128.47, 130.72, 132.01, 133.32, 139.67, 144.69, 157.02, 157.56, 182.76 ppm; HRMS: m/z calcd. for $C_{22}H_{25}N_2O_3Si$: 393.1634 $[M+H]^+$, found 393.1631.

1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]-thiepino[4,5-*d*]imidazole-2-carbaldehyde (7f). Obtained from **4f** as a yellowish solid: Yield 74%; mp 82.94°C; IR (ATR): 2951, 1687, 1445, 1420, 1083, 831, 760 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.88 (t, J = 8.24 Hz, 2H), 3.51 (td, J = 9.08, 7.78 Hz, 1H), 3.66 (td, J = 9.08, 8.09 Hz, 1H), 5.87–5.93 (m, 1H), 5.93–6.00 (m, 1H), 7.53–7.63 (m, 2H), 7.63–7.66 (m, 2H), 7.75 (dd, J = 7.78, 1.37 Hz, 1H), 7.86–7.95 (m, 2H), 7.97 (dd, J = 7.63, 1.53 Hz, 1H), 10.04 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.14, 17.58, 66.23, 73.80, 128.82, 129.61, 129.64, 129.97, 131.09, 131.11, 132.78, 134.31, 134.58, 136.05, 136.52, 136.70, 143.11, 143.79, 182.87 ppm; HRMS: m/z calcd. for $C_{22}H_{25}N_2O_2SiS$: 409.1406 $[M+H]^+$, found 409.1398.

11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole-2-carbaldehyde (7g). Obtained from **5a** as a yellowish solid: Yield 78%; mp 94.58°C; IR (ATR): 2952, 1684, 1449, 1215, 1073, 824, 772 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.94–0.99 (m, 2H), 3.74–3.80 (m, 2H), 5.90 (s, 2H), 7.37–7.42 (m, 1H), 7.49–7.54 (m, 2H), 7.61–7.68 (m, 2H), 7.87 (ddd, J = 7.48, 1.22, 1.07 Hz, 1H), 8.08 (d, J = 2.44 Hz, 1H), 9.96 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.03, 17.76, 66.45, 73.50, 121.70, 123.34, 124.78, 126.22, 126.50, 127.44, 127.77, 130.49, 130.97, 131.49, 131.90, 140.12, 144.81, 156.01, 156.74, 182.96 ppm; HRMS: m/z calcd. for $C_{22}H_{24}N_2O_3SiCl$: 427.1245 $[M+H]^+$, found 427.1228.

11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole-2-carbaldehyde (7h). Obtained from **5b** as an amorphous yellowish solid: Yield 78%; IR (ATR): 2951, 1690, 1248, 1081, 832, 762 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.89–0.93 (m, 2H), 3.55–3.64 (m, 1H), 3.64–3.72 (m, 1H), 5.75 (d, J = 10.68 Hz, 1H), 5.99 (d, J = 10.68 Hz, 1H), 7.52–7.61 (m, 2H), 7.66–7.73 (m, 2H), 7.85 (d, J = 8.54 Hz, 1H), 7.94 (dd, J = 7.78, 1.37 Hz, 1H), 8.04 (d, J = 2.44 Hz, 1H), 10.02 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.09, 17.71, 66.21, 73.79, 128.93, 129.26, 129.84, 130.20, 130.74, 132.83, 132.88, 134.10, 134.45, 134.63, 135.05, 135.77, 136.53, 143.53, 143.88, 183.02 ppm; HRMS: m/z calcd. for $C_{22}H_{24}N_2O_2SiSCl$: 443.1016 $[M+H]^+$, found 443.1005.

5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazole-2-carbaldehyde (7i). Obtained from **6a** as a yellowish solid: Yield 83%; mp 113.81°C; IR (ATR): 2946, 1688, 1238, 1211, 1083, 825, 773 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.92–0.99 (m, 2H), 3.72–3.79 (m, 2H), 5.92 (s, 2H), 7.43–7.49 (m, 1H), 7.54–7.59 (m, 2H), 7.59–7.67 (m, 2H), 7.83 (dd, J = 2.29, 0.76 Hz, 1H), 8.01–8.05 (m, 1H), 9.96 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ –1.08, 17.71, 66.51, 73.70, 121.23, 123.07, 123.70, 126.51, 126.63, 128.32, 128.55, 130.29, 130.33, 132.26, 133.73, 138.24, 144.82, 155.53, 157.19, 182.77 ppm; HRMS: m/z calcd. for $C_{22}H_{24}N_2O_3ClSi$: 427.1245 $[M+H]^+$, found 427.1229.

5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazole-2-carbaldehyde (7j). Obtained from **6b** as an amorphous yellowish solid: Yield 62%; IR (ATR): 2950, 1688, 1434, 1247, 1084, 833, 767 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.85–0.91 (m, 2H), 3.52 (td, J = 9.00, 7.63 Hz, 1H), 3.66 (td, J = 9.16, 7.93 Hz, 1H), 5.88–5.93 (m, 1H), 5.93–5.99 (m, 1H), 7.61 (dd, J = 8.24, 2.44 Hz, 1H), 7.64–7.69 (m, 2H), 7.76 (d, J = 8.54 Hz, 1H), 7.87–7.97 (m, 3H), 10.05 ppm (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.14, 17.58, 66.29, 73.91, 128.09, 129.65, 129.87, 130.07, 130.94, 131.34, 133.31, 134.36, 134.40, 134.44, 135.38, 136.93, 138.44, 141.74, 143.94, 182.88 ppm; HRMS: m/z calcd. for $C_{22}H_{24}N_2O_2SiSCl$: 443.1016 $[M+H]^+$, found 443.1002.

General procedure for reduction of aldehydes 7 (preparation of compounds 8). To a solution of **7** (0.34 g, 1.23 mmol) in mixture of methanol (15 mL) and dichloromethane (45 mL) sodium borohydride (0.074 g, 1.97 mmol) was added portionwise. The reaction mixture was stirred for 2 h at room temperature, pH adjusted to 5–6, concentrated, diluted with water (50 mL), and extracted with dichloromethane (3 × 30 mL). The organic extract was washed with saturated sodium hydrogencarbonate (50 mL), dried over anhydrous sodium sulfate and evaporated to give compound **8**.

(1-Methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl)methanol (8a). Obtained from **7a** as a white solid: Yield 97%; mp 237.31°C; IR (ATR): 3184, 2923, 1515, 1196, 1024, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.88 (s, 3H), 4.67 (d, J = 5.80 Hz, 2H), 5.52 (t, J = 5.65 Hz, 1H), 7.22–7.27 (m, 1H), 7.29–7.38 (m, 3H), 7.42 (td, J = 7.63, 1.53 Hz, 1H), 7.45–7.49 (m, 1H), 7.62 (dd, J = 7.78, 1.68 Hz, 1H), 7.72 ppm (dd, J = 8.09, 1.68 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 32.81, 56.46, 121.46, 122.65, 123.41, 125.76, 125.88, 126.59, 126.72, 127.95, 128.09, 129.10, 129.61, 135.65, 150.62, 155.84, 156.01 ppm; HRMS: m/z calcd. for $C_{17}H_{14}N_2O_2Na$: 301.0953 $[M+Na]^+$, found 301.0957.

(1-Methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl)methanol (8b). Obtained from **7b** as a white solid: Yield 77%; mp 182.69°C; IR (ATR): 3179, 2957, 2919, 1451, 1375, 1031, 1018, 759, 741, 719 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, 3H), 4.66–4.74 (m, 2H), 5.55 (t, J = 5.65 Hz, 1H), 7.31–7.38 (m, 1H), 7.38–7.51 (m, 3H), 7.54–7.60 (m, 2H), 7.70 (dd, J = 7.78, 1.07 Hz, 1H), 7.78 ppm (dd, J = 7.63, 1.53 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 32.73, 56.57, 128.10, 128.45, 128.70, 129.12, 129.17, 129.26, 131.67, 132.51, 132.71, 133.22, 133.90, 134.08, 138.25, 139.56, 149.69 ppm; HRMS: m/z calcd. for $C_{17}H_{14}N_2OSNa$: 317.0725 $[M+Na]^+$, found 317.0716.

[1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methanol (8c). Obtained from **7c** as a white solid: Yield 98%; mp 169.09°C; IR (ATR): 3119, 3059, 3030, 1513, 1451, 1207, 1029, 763, 738, 696 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.94 (t, J = 7.48 Hz, 2H), 4.49 (d, J = 5.49 Hz, 2H), 4.60 (t, J = 7.63 Hz, 2H), 5.57–5.60 (m, 1H), 7.08–7.11 (m, 2H), 7.17–7.27 (m, 4H), 7.32–7.39 (m, 3H), 7.41–7.50 (m, 2H), 7.68–7.76 ppm (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.26, 46.43, 56.56, 121.39, 122.72, 123.69, 125.75, 126.01, 126.07, 126.78, 126.98, 128.07, 128.81, 128.95, 129.23, 129.72, 136.50, 138.12, 150.84, 156.00, 156.35 ppm; HRMS: m/z calcd. for $C_{24}H_{20}N_2O_2Na$: 391.1422 $[M+Na]^+$, found 391.1423.

[1-(2-Phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methanol (8d). Obtained from **7d** as a white solid: Yield 97%; mp 188.04°C; IR (ATR): 3162, 1454, 1418, 1036, 754, 715, 692 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.68–2.83 (m, 2H), 4.29 (d, J = 13.12 Hz, 1H), 4.42–4.54 (m, 2H), 4.62–4.71 (m, 1H), 5.59 (br. s., 1H), 6.97–7.03 (m, 2H), 7.13–7.23 (m, 3H), 7.32–7.53 (m, 4H), 7.58 (dd, J = 7.78, 1.37 Hz, 1H), 7.66–7.78 ppm (m, J = 16.25, 16.25, 7.63, 1.37 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.24, 46.31, 56.46, 126.89, 127.80, 128.21, 128.75, 128.97, 129.12, 129.30, 129.37, 130.79, 132.50, 133.03, 133.91, 134.62, 138.08, 138.21, 140.51, 149.91 ppm; HRMS: m/z calcd. for $C_{24}H_{21}N_2OS$: 385.1375 $[M+H]^+$, found 385.1375.

[1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methanol (8e). Obtained from **7e** as a white solid: Yield 99%; mp 147.68°C; IR (ATR): 3189, 2951, 2893, 1450, 1210, 1080, 835, 765, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.92–0.98 (m, 2H), 3.67–3.73 (m, 2H), 4.76 (d, J = 5.80 Hz, 2H), 5.63 (s, 2H), 5.69 (t, J = 5.80 Hz, 1H), 7.28–7.37 (m, 2H), 7.38–7.44 (m, 2H), 7.45–7.54 (m, 2H), 7.75–7.81 (m, 1H), 7.84 ppm (dd, J = 7.93, 1.53 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.06, 17.68, 56.48, 65.96, 73.15, 121.47, 122.65, 123.30, 125.80, 125.98, 126.82, 127.10, 127.78, 128.06, 129.45, 130.00, 136.08, 151.14, 156.21 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}N_2O_3SiNa$: 417.1610 [M+Na]$^+$, found 417.1591.

[1-({[2-(Trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]-thiepino[4,5-*d*]imidazol-2-yl]methanol (8f). Obtained from **7f** as a white amorphous solid: Yield 98%; IR (ATR): 3195, 3051, 2952, 1487, 1249, 1082, 1033, 858, 835, 760, 740 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.84–0.91 (m, 2H), 3.40–3.47 (m, 1H), 3.59–3.66 (m, 1H), 4.78–4.86 (m, 2H), 5.58–5.65 (m, 1H), 5.65–5.72 (m, 1H), 5.75 (t, J = 5.65 Hz, 1H), 7.43–7.48 (m, 1H), 7.50–7.60 (m, 3H), 7.67 (dd, J = 7.63, 1.22 Hz, 1H), 7.74 (dd, J = 7.48, 1.68 Hz, 1H), 7.80 (dd, J = 7.63, 1.53 Hz, 1H), 7.88 ppm (dd, J = 7.63, 1.53 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.12, 17.58, 56.58, 65.75, 73.13, 128.32, 128.75, 129.01, 129.20, 129.32, 129.60, 131.90, 132.54, 132.69, 133.58, 133.90, 134.58, 137.86, 139.89, 150.40 ppm; HRMS: *m/z* calcd. for $C_{22}H_{27}N_2O_2SSi$: 411.1563 [M+H]$^+$, found 411.1548.

[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methanol (8g). Obtained from **7g** as a white amorphous solid: Yield 100%; IR (ATR): 3179, 2951, 1491, 1446, 1248, 1211, 1076, 1031, 828, 773, 741 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.93–1.02 (m, 2H), 3.69–3.77 (m, 2H), 4.73 (d, J = 5.80 Hz, 2H), 5.58 (s, 2H), 5.69 (t, J = 5.65 Hz, 1H), 7.26–7.34 (m, 1H), 7.37–7.44 (m, 2H), 7.47–7.55 (m, 2H), 7.72–7.78 (m, 1H), 7.91 ppm (d, J = 2.44 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.02, 17.80, 56.36, 65.93, 73.08, 121.47, 124.35, 125.08, 126.08, 126.42, 126.81, 126.94, 127.43, 129.51, 129.79, 130.19, 136.90, 151.50, 154.65, 155.95 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}ClN_2O_3Si$: 429.1401 [M+H]$^+$, found 429.1398.

[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methanol (8h). Obtained from **7h** as a white amorphous solid: Yield 99%; IR (ATR): 3191, 3070, 2952, 2923, 2889, 1581, 1480, 1366, 1249, 1078, 1030, 858, 835, 769, 736 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.90–0.97 (m, 2H), 3.53 (td, J = 9.00, 7.93 Hz, 1H), 3.60–3.72 (m, 1H), 4.77 (d, J = 5.80 Hz, 2H), 5.44 (d, J = 10.99 Hz, 1H), 5.66 (d, J = 10.99 Hz, 1H), 5.72 (t, J = 5.65 Hz, 1H), 7.41–7.52 (m, 2H), 7.55 (dd, J = 8.39, 2.29 Hz, 1H), 7.63 (dd, J = 7.63, 1.22 Hz, 1H), 7.75 (d, J = 8.24 Hz, 1H), 7.81–7.87 ppm (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.79, 56.42, 65.72, 73.11, 127.97, 128.46, 129.28, 129.32, 129.42, 130.50, 132.58, 133.09, 134.19, 134.43, 135.37, 137.65, 140.63, 150.67 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}ClN_2O_2SSi$: 445.1173 [M+H]$^+$, found 445.1157.

[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methanol (8i). Obtained from **7i** as a white amorphous solid: Yield 93%; IR (ATR): 3203, 3066, 2953, 2895, 1496, 1446, 1249, 1216, 10991, 1081, 856, 835, 771, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 3.67–3.73 (m, 2H), 4.76 (d, J = 5.80 Hz, 2H), 5.64 (s, 2H), 5.72 (t, J = 5.80 Hz, 1H), 7.35–7.41 (m, 1H), 7.44–7.56 (m, 4H), 7.71 (dd, J = 1.98, 0.76 Hz, 1H), 7.86 ppm (dd, J = 7.78, 1.37 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.67, 56.45, 66.03, 73.24, 122.69, 122.94, 123.42, 125.93, 126.30, 127.23, 128.76, 129.00, 129.59, 129.91, 130.34, 134.79, 151.49, 154.69, 155.87 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}ClN_2O_3Si$: 429.1401 [M+H]$^+$, found 429.1395.

[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methanol (8j). Obtained from **7j** as a white amorphous solid: Yield 99%; IR (ATR): 3184, 3059, 2951, 1582, 1483, 1247, 1080, 1036, 834, 766, 749 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.82–0.93 (m, 2H), 3.43–3.54 (m, 1H), 3.54–3.66 (m, 1H), 4.82 (dd, J = 5.65, 2.29 Hz, 2H), 5.59–5.66 (m, 1H), 5.66–5.74 (m, 1H), 5.77 (t, J = 5.65 Hz, 1H), 7.52 (dd, J = 8.24, 2.44 Hz, 1H), 7.54–7.62 (m, 2H), 7.69 (d, J = 8.24 Hz, 1H), 7.75–7.82 (m, 2H), 7.83 ppm (d, J = 2.44 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.13, 17.57, 56.53, 65.82, 73.23, 127.52, 128.68, 128.87, 129.61, 129.94, 132.26, 132.46, 132.58, 133.90, 133.95, 134.03, 134.17, 138.65, 139.60, 150.75 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}ClN_2O_2SSi$: 445.1173 [M+H]$^+$, found 445.1164.

General procedure for preparation of compounds 9. To a 40% aq sodium hydroxide (1.66 mL) solution of **8** (60 mg, 0.216 mmol) in toluene (2.8 mL), appropriate ω-chloroalkyldimethylamine (0.862 mmol), and a catalytic amount of benzyltriethylammonium chloride were added. Reaction mixture was heated at reflux until TLC indicated the reaction was complete, and then cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (3 × 15 mL). The organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate, and evaporated. After purification on silica gel SPE cartridge using step gradient system for elution *n*-hexane/(ethyl acetate/*n*-hexane/diethylamine 10:10:1.5) compound **9** was isolated.

Dimethyl(2-{[(1-methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl)methyl]oxy}ethyl)amine (9a). Obtained from **8a** as a yellowish amorphous solid: Yield 59%; IR (ATR): 3059, 2939, 2859, 2820, 2770, 1516, 1496, 1456, 1444, 1207, 1106, 1090, 1029, 762, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 6H), 2.45 (t, J = 5.95 Hz, 2H), 3.61 (t, J = 5.95 Hz, 2H), 3.87 (s, 3H), 4.69 (s, 2H), 7.22–7.28 (m, 1H), 7.30–7.39 (m, 3H), 7.41–7.50 (m, 2H), 7.63 (dd, J = 7.78, 1.68 Hz, 1H), 7.70–7.75 ppm (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 32.77, 45.86, 58.61, 64.80, 68.31, 121.48, 122.67, 123.22, 125.81, 125.91, 126.67, 126.86, 127.89, 128.30, 129.26, 129.80, 135.88, 147.59, 155.92, 156.06 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3O_2$: 350.1869 [M+H]$^+$, found 350.1854.

Dimethyl(3-{[(1-methyl-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl)methyl]oxy}propyl)amine (9b). Obtained from **8a** as a yellowish amorphous solid: Yield 80%; IR (ATR): 3062, 2944, 2859, 2817, 2768, 1517, 1497, 1458, 1444, 1207, 1089, 798, 763, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.68 (quin, J = 6.79 Hz, 2H), 2.10 (s, 6H), 2.26 (t, J = 7.17 Hz, 2H), 3.55 (t, J = 6.41 Hz, 2H), 3.87 (s, 3H), 4.66 (s, 2H), 7.22–7.28 (m, 1H), 7.30–7.50 (m, 5H), 7.64 (dd, J = 7.93, 1.53 Hz, 1H), 7.68–7.75 ppm (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.65, 32.75, 45.54, 56.30, 64.85, 68.58, 121.48, 122.66, 123.22, 125.80, 125.91, 126.67, 126.88, 127.88, 128.30, 129.26, 129.80, 135.87, 147.64, 155.93, 156.06 ppm; HRMS: *m/z* calcd. for $C_{22}H_{26}N_3O_2$: 364.2025 [M+H]$^+$, found 364.2014.

Dimethyl(2-{[(1-methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)amine (9c). Obtained from **8b** as a yellowish amorphous solid: Yield 62%; IR (ATR): 3051, 2940, 2859, 2819, 2770, 1487, 1452, 1103, 1031, 759, 741 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.16 (s, 6H), 2.46 (t, J = 5.80 Hz, 2H), 3.58–3.69 (m, 2H), 3.79 (d, J = 0.92 Hz, 3H), 4.68–4.75 (m, 2H), 7.32–7.52 (m, 4H), 7.55–7.61 (m, 2H), 7.69–7.74 (m, 1H), 7.74–7.81 ppm (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 32.69, 45.88, 58.65, 64.96, 68.40, 128.19, 128.57, 128.79, 129.15, 129.20, 129.39, 131.96, 132.52, 132.55, 133.34, 133.93, 134.22, 138.10, 139.79, 146.71 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3OS$: 366.1640 [M+H]$^+$, found 366.1628.

Dimethyl(3-{[(1-methyl-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)amine (9d). Obtained from **8b** as a yellowish amorphous solid: Yield 80%; IR (ATR): 3051, 2943, 2857, 2816, 2766, 1487, 1453, 1092, 1030, 759, 741 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.70 (quin, J = 6.82 Hz, 2H), 2.11 (s, 6 H), 2.27 (t, J = 7.32 Hz, 2H), 3.53–3.62 (m, 2H), 3.79 (s, 3H), 4.65–4.72 (m, 2H), 7.32–7.52 (m, 4H), 7.59 (ddd, J = 10.83, 7.63, 1.37 Hz, 2H), 7.71 (dd, J = 7.63, 1.53 Hz, 1H), 7.78 ppm (dd, J = 7.63, 1.53 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.68, 32.69, 45.57, 56.32, 65.01, 68.70, 128.18, 128.59, 128.80, 129.14, 129.19, 129.39, 131.96, 132.52, 132.55, 133.33, 133.92, 134.20, 138.09, 139.76, 146.76 ppm; HRMS: *m/z* calcd. for $C_{22}H_{25}N_3OSNa$: 402.1616 [M+Na]$^+$, found 402.1610.

Dimethyl[2-({[1-(2-phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9e). Obtained from **8c** as a yellowish amorphous solid: Yield 72%; IR (ATR): 3062, 3025, 2939, 2860, 2819, 2769, 1513, 1495, 1450, 1207, 1095, 1037, 760, 743, 699 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 6H), 2.45 (t, J = 5.80 Hz, 2H), 2.94 (t, J = 7.63 Hz, 2H), 3.59 (t, J = 5.80 Hz, 2H), 4.53 (s, 2H), 4.57 (t, J = 7.48 Hz, 2H), 7.08–7.13 (m, 2H), 7.17–7.28 (m, 4H), 7.32–7.40 (m, 3H), 7.42–7.50 (m, 2H), 7.69–7.77 ppm (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.20, 45.87, 46.44, 58.67, 64.82, 68.27, 121.40, 122.75, 123.49, 125.79, 126.09, 126.16, 126.86, 127.01, 127.34, 127.87, 128.84, 128.94, 129.38, 129.91, 136.73, 138.02, 147.68, 156.11, 156.41 ppm; HRMS: *m/z* calcd. for $C_{28}H_{30}N_3O_2$: 440.2338 [M+H]$^+$, found 440.2325.

Dimethyl[3-({[1-(2-phenylethyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9f). Obtained from **8c** as a yellowish amorphous solid: Yield 52%; IR (ATR): 3059, 3025, 2942, 2859, 2816, 2766, 1513, 1495, 1450, 1207, 1092, 761, 743, 699 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.68 (quin, J = 6.72 Hz, 2H), 2.07 (s, 6H), 2.25 (t, J = 7.17 Hz, 2H), 2.94 (t, J = 7.63 Hz, 2H), 3.53 (t, J = 6.41 Hz, 2H), 4.50 (s, 2H), 4.57 (t, J = 7.48 Hz, 2H), 7.08–7.12 (m, 2H), 7.18–7.28 (m, 4H), 7.32–7.40 (m, 3H), 7.42–7.50 (m, 2H), 7.69–7.76 ppm (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.69, 36.23, 45.51, 46.43, 56.34, 64.90, 68.69, 121.40, 122.75, 123.48, 125.78, 126.08, 126.17, 126.86, 127.04, 127.36, 127.86, 128.85, 128.91, 129.38, 129.91, 136.70, 137.98, 147.70, 156.12, 156.41 ppm; HRMS: *m/z* calcd. for $C_{29}H_{32}N_3O_2$: 454.2495 [M+H]$^+$, found 454.2498.

Dimethyl[2-({[1-(2-phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9g). Obtained from **8d** as a yellowish amorphous solid: Yield 44%; IR (ATR): 3055, 2939, 2859, 2818, 2768, 1485, 1454, 1422, 1109, 1057, 1032, 758, 741, 698 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (s, 6H), 2.45 (t, J = 5.80 Hz, 2H), 2.68–2.83 (m, 2H), 3.53–3.64 (m, 2H), 4.34 (d, J = 12.51 Hz, 1H), 4.37–4.46 (m, 1H), 4.54 (d, J = 12.21 Hz, 1H), 4.66 (ddd, J = 14.19, 8.24, 5.34 Hz, 1H), 6.98–7.03 (m, 2H), 7.14–7.23 (m, 3H), 7.33–7.53 (m, 4H), 7.59 (dd, J = 7.78, 1.37 Hz, 1H), 7.67–7.78 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 36.17, 45.88, 46.33, 58.68, 64.84, 68.30, 126.92, 127.93, 128.30, 128.77, 128.84, 128.96, 129.15, 129.39, 129.42, 131.10, 132.51, 132.86, 133.93, 134.03, 134.80, 138.00, 138.05, 140.73, 146.74 ppm; HRMS: *m/z* calcd. for $C_{28}H_{30}N_3OS$: 456.2110 [M+H]$^+$, found 456.2095.

Dimethyl[3-({[1-(2-phenylethyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9h). Obtained from **8d** as a yellowish amorphous solid: Yield 65%; IR (ATR): 3055, 3025, 2941, 2857, 2815, 2765, 1485, 1455, 1432, 1089, 1078, 758, 741, 698 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.68 (quin, J = 6.79 Hz, 2H), 2.09 (s, 6H), 2.21–2.32 (m, 2H), 2.68–2.84 (m, 2H), 3.46–3.59 (m, 2H), 4.29 (d, J = 12.51 Hz, 1H), 4.39 (ddd, J = 14.88, 7.78, 7.55 Hz, 1H), 4.53 (d, J = 12.21 Hz, 1H), 4.62–4.71 (m, 1H), 6.98–7.02 (m, 2H), 7.14–7.22 (m, 3H), 7.33–7.38 (m, 1H), 7.40–7.47 (m, 2H), 7.50 (td, J = 7.55, 1.37 Hz, 1H), 7.59 (dd, J = 7.63, 1.22 Hz, 1H), 7.67–7.77 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.67, 36.21, 45.52, 46.33, 56.34, 64.92, 68.74, 126.94, 127.94, 128.30, 128.79, 128.85, 128.93, 129.14, 129.37, 129.42, 131.12, 132.51, 132.84, 133.93, 134.03, 134.79, 137.96, 138.02, 140.69, 146.78 ppm; HRMS: *m/z* calcd. for $C_{29}H_{32}N_3OS$: 470.2266 [M+H]$^+$, found 470.2253.

Dimethyl[2-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9i). Obtained from **8e** as a yellowish amorphous solid: Yield 74%; IR (ATR): 2949, 2893, 2851, 2819, 2769, 1450, 1248, 1210, 1077, 856, 834, 763, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ −0.01 (br. s., 9H), 0.94 (t, J = 7.93 Hz, 2H), 2.20 (s, 6H), 2.49 (t, J = 5.95 Hz, 2H), 3.63–3.73 (m, 4H), 4.77 (s, 2H), 5.59 (s, 2H), 7.27–7.38 (m, 2H), 7.38–7.45 (m, 2H), 7.45–7.55 (m, 2H), 7.73–7.80 (m, 1H), 7.81–7.88 ppm (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.04, 17.74, 45.90, 58.62, 64.74, 65.99, 68.42, 73.32, 121.48, 122.68, 122.71, 123.15, 125.85, 126.02, 126.90, 127.20, 127.62, 128.37, 129.59, 130.17, 136.32, 147.98, 156.27 ppm; HRMS: *m/z* calcd. for $C_{26}H_{36}N_3O_3Si$: 466.2526 [M+H]$^+$, found 466.2529.

Dimethyl[3-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]amine (9j). Obtained from **8e** as a yellowish amorphous solid: Yield 83%; IR (ATR): 2949, 2855, 2815, 2765, 1450, 1210, 1075, 857, 833, 764, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.91–0.99 (m, 2H), 1.72 (quin, J = 6.82 Hz, 2H), 2.14 (s, 6H), 2.29 (t, J = 7.17 Hz, 2H), 3.60 (t, J = 6.41 Hz, 2H), 3.66–3.73 (m, 2H), 4.73 (s, 2H), 5.58 (s, 2H), 7.27–7.38 (m, 2H), 7.38–7.44 (m, 2H), 7.45–7.54 (m, 2H), 7.74–7.79 (m, 1H), 7.84 ppm (dd, J = 7.93, 1.22 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.74, 27.66, 45.55, 56.31, 64.84, 66.02, 68.80, 73.30, 121.48, 122.68, 123.15, 125.83, 126.01, 126.90, 127.19, 127.62, 128.39, 129.58, 130.17, 136.29, 148.01, 156.27 ppm; HRMS: *m/z* calcd. for $C_{27}H_{38}N_3O_3Si$: 480.2682 [M+H]$^+$, found 480.2692.

Dimethyl[2-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]amine (9k). Obtained from **8f** as a yellowish amorphous solid: Yield

61%; IR (ATR): 2949, 2897, 2863, 2818, 2768, 1485, 1461, 1365, 1248, 1077, 1037, 833, 759 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.84–0.91 (m, 2H), 2.25 (s, 6H), 2.55 (t, J = 5.95 Hz, 2H), 3.38–3.48 (m, 1H), 3.58–3.66 (m, 1H), 3.69–3.78 (m, 2H), 4.78–4.87 (m, 2H), 5.55 (d, J = 10.99 Hz, 1H), 5.67 (d, J = 10.99 Hz, 1H), 7.42–7.48 (m, 1H), 7.49–7.59 (m, 3H), 7.67 (d, J = 7.63 Hz, 1H), 7.73–7.82 (m, 2H), 7.87 ppm (dd, J = 7.78, 1.37 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.12, 17.63, 45.91, 58.64, 64.88, 65.77, 68.55, 73.31, 128.39, 128.83, 129.09, 129.22, 129.34, 129.71, 132.14, 132.54, 132.56, 133.71, 133.93, 134.67, 137.72, 140.13, 147.25 ppm; HRMS: m/z calcd. for $C_{26}H_{36}N_3O_2SSi$: 482.2298 $[M+H]^+$, found 482.2314.

Dimethyl[3-({[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methyl}oxy)propyl]amine (9l). Obtained from **8f** as a yellowish amorphous solid: Yield 82%; IR (ATR): 2949, 2859, 2815, 2764, 1485, 1461, 1248, 1076, 833, 759, 694 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 1.78 (quin J = 6.79 Hz, 2H), 2.19 (s, 6H), 2.31–2.40 (m, 2H), 3.37–3.49 (m, 1H), 3.58–3.71 (m, 3H), 4.74–4.84 (m, 2H), 5.53 (d, J = 11.29 Hz, 1H), 5.66 (d, J = 11.29 Hz, 1H), 7.42–7.49 (m, 1H), 7.49–7.60 (m, 3H), 7.67 (dd, J = 7.63, 1.22 Hz, 1H), 7.78 (ddd, J = 18.16, 7.48, 1.53 Hz, 2H), 7.87 ppm (dd, J = 7.78, 1.37 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.14, 17.64, 27.68, 45.57, 56.32, 64.96, 65.80, 68.92, 73.31, 128.40, 128.84, 129.09, 129.22, 129.33, 129.72, 132.15, 132.54, 132.56, 133.70, 133.93, 134.66, 137.70, 140.09, 147.30 ppm; HRMS: m/z calcd. for $C_{27}H_{38}N_3O_2SSi$: 482.2298 $[M+H]^+$, found 482.2314.

[2-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9m). Obtained from **8g** as a yellowish amorphous solid: Yield 72%; IR (ATR): 2949, 2893, 2859, 2819, 2769, 1491, 1446, 1248, 1211, 1075, 830, 773, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.94–1.00 (m, 2H), 2.19 (s, 6H), 2.48 (t, J = 5.80 Hz, 2H), 3.65 (t, J = 5.80 Hz, 2H), 3.68–3.76 (m, 2H), 4.75 (s, 2H), 5.55 (s, 2H), 7.27–7.34 (m, 1H), 7.41 (d, J = 3.66 Hz, 2H), 7.49–7.55 (m, 2H), 7.75 (dd, J = 7.02, 0.61 Hz, 1H), 7.92 ppm (d, J = 2.14 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.02, 17.87, 45.83, 58.55, 64.58, 65.93, 68.35, 73.24, 121.48, 124.38, 124.93, 126.11, 126.52, 127.01, 127.14, 127.27, 129.68, 129.91, 130.20, 137.12, 148.37, 154.71, 156.01 ppm; HRMS: m/z calcd. for $C_{26}H_{35}ClN_3O_3Si$: 500.2136 $[M+H]^+$, found 500.2136.

[3-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9n). Obtained from **8g** as a yellowish amorphous solid: Yield 85%; IR (ATR): 2950, 2860, 2816, 2765, 1492, 1446, 1249, 1212, 1074, 857, 831, 772, 742 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.94–1.00 (m, 2H), 1.70 (quin, J = 6.79 Hz, 2H), 2.12 (s, 6H), 2.27 (t, J = 7.17 Hz, 2H), 3.57 (t, J = 6.41 Hz, 2H), 3.68–3.75 (m, 2H), 4.71 (s, 2H), 5.53 (s, 2H), 7.28–7.33 (m, 1H), 7.41 (d, J = 3.66 Hz, 2H), 7.49–7.55 (m, 2H), 7.74–7.77 (m, 1H), 7.92 ppm (d, J = 2.14 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.04, 17.86, 27.62, 45.52, 56.28, 64.69, 65.96, 68.81, 73.23, 121.49, 124.38, 124.92, 126.11, 126.50, 127.02, 127.15, 127.25, 129.68, 129.91, 130.20, 137.08, 148.43, 154.71, 156.01 ppm; HRMS: m/z calcd. for $C_{27}H_{37}ClN_3O_3Si$: 514.2293 $[M+H]^+$, found 514.2288.

[2-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9o). Obtained from **8h** as a yellowish amorphous solid: Yield 62%; IR (ATR): 2949, 2893, 2863, 2863, 2768, 1580, 1479, 1460, 1364, 1248, 1101, 1076, 1030, 833, 769, 744 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.88–0.96 (m, 2H), 2.21 (s, 6H), 2.50 (t, J = 5.80 Hz, 2H), 3.52 (td, J = 9.16, 7.93 Hz, 1H), 3.62–3.74 (m, 3H), 4.78 (s, 2H), 5.41 (d, J = 10.99 Hz, 1H), 5.63 (d, J = 10.68 Hz, 1H), 7.41–7.53 (m, 2H), 7.56 (dd, J = 8.39, 2.29 Hz, 1H), 7.63 (dd, J = 7.63, 1.22 Hz, 1H), 7.76 (d, J = 8.54 Hz, 1H), 7.83 (dd, J = 7.63, 1.53 Hz, 1H), 7.87 ppm (d, J = 2.14 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.82, 45.90, 58.62, 64.68, 65.71, 68.55, 73.28, 128.07, 128.53, 129.41, 129.46, 130.77, 132.59, 133.19, 133.23, 134.21, 134.30, 135.39, 137.49, 140.83, 147.58 ppm; HRMS: m/z calcd. for $C_{26}H_{35}ClN_3O_2SSi$: 516.1908 $[M+H]^+$, found 516.1909.

[3-({[11-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]thiepino[4,5-*d*]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9p). Obtained from **8h** as a yellowish amorphous solid: Yield 77%; IR (ATR): 2949, 2859, 2815, 2765, 1581, 1461, 1365, 1248, 1075, 1029, 857, 833, 769, 744 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.89–0.98 (m, 2H), 1.74 (quin, J = 6.79 Hz, 2H), 2.15 (s, 6H), 2.26–2.37 (m, 2H), 3.47–3.56 (m, 1H), 3.58–3.72 (m, 3H), 4.71–4.80 (m, 2H), 5.41 (d, J = 10.99 Hz, 1H), 5.62 (d, J = 10.99 Hz, 1H), 7.41–7.53 (m, 2H), 7.56 (dd, J = 8.24, 2.14 Hz, 1H), 7.63 (dd, J = 7.63, 1.22 Hz, 1H), 7.76 (d, J = 8.24 Hz, 1H), 7.83 (dd, J = 7.63, 1.53 Hz, 1H), 7.87 ppm (d, J = 2.44 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.09, 17.82, 27.66, 45.56, 56.30, 64.78, 65.74, 68.91, 73.29, 128.07, 128.53, 129.41, 129.46, 130.79, 132.60, 133.19, 133.22, 134.21, 134.30, 135.39, 137.48, 137.50, 140.80, 147.64 ppm; HRMS: m/z calcd. for $C_{27}H_{37}ClN_3O_2SSi$: 530.2064 $[M+H]^+$, found 530.2061.

[2-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9r). Obtained from **8i** as a yellowish amorphous solid: Yield 74%; IR (ATR): 2949, 2893, 2859, 2814, 2765, 1495, 1445, 1213, 1098, 1075, 853, 828, 769, 745 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 2.20 (s, 6H), 2.50 (t, J = 5.80 Hz, 2H), 3.63–3.74 (m, 4H), 4.77 (s, 2H), 5.61 (s, 2H), 7.34–7.41 (m, 1H), 7.44–7.57 (m, 4H), 7.70–7.73 (m, 1H), 7.87 ppm (dd, J = 7.78, 1.37 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.07, 17.72, 45.89, 58.61, 64.67, 66.06, 68.45, 73.42, 122.72, 122.80, 123.43, 126.01, 126.32, 127.32, 129.07, 129.12, 129.43, 129.95, 130.49, 135.03, 148.33, 154.76, 155.94 ppm; HRMS: m/z calcd. for $C_{26}H_{35}ClN_3O_3Si$: 500.2136 $[M+H]^+$, found 500.2135.

[3-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-dibenzo[2,3:6,7]oxepino[4,5-*d*]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9s). Obtained from **8i** as a yellowish amorphous solid: Yield 81%; IR (ATR): 2949, 2855, 2816, 2765, 1495, 1478, 1445, 1247, 1213, 1074, 854, 828, 769 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.91–0.98 (m, 2H), 1.73 (quin, J = 6.82 Hz, 2H), 2.14 (s, 6 H), 2.30 (t, J = 7.17 Hz, 2H), 3.60 (t, J = 6.41 Hz, 2H), 3.67–3.73 (m, 2H), 4.74 (s, 2H), 5.59 (s, 2H), 7.38 (ddd, J = 7.78, 7.02, 1.37 Hz, 1H), 7.44–7.57 (m, 4H), 7.71 (t, J = 0.92 Hz, 1H), 7.86 ppm (dd, J = 7.78, 1.37 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.08, 17.72, 27.65, 45.54, 56.30, 64.74, 66.09, 68.83, 73.40, 122.72, 122.79, 123.43, 126.01, 126.32, 127.32, 129.08, 129.13, 129.42, 129.95, 130.51, 135.00, 148.38, 154.75, 155.94 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_3Si$: 514.2293 $[M+H]^+$, found 514.2296.

[2-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)ethyl]dimethylamine (9t). Obtained from **8j** as a yellowish amorphous solid: Yield 82%; IR (ATR): 2949, 2889, 2859, 2765, 1582, 1482, 1456, 1248, 1078, 1038, 834, 765, 748 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.84–0.92 (m, 2H), 2.26 (s, 6H), 2.56 (t, J = 5.80 Hz, 2H), 3.40–3.48 (m, 1H), 3.58–3.66 (m, 1H), 3.69–3.78 (m, 2H), 4.78–4.88 (m, 2H), 5.57 (d, J = 11.29 Hz, 1H), 5.68 (d, J = 10.99 Hz, 1H), 7.50–7.62 (m, 3H), 7.69 (d, J = 8.24 Hz, 1H), 7.76–7.85 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.14, 17.60, 45.89, 58.62, 64.80, 65.84, 68.58, 73.42, 127.59, 128.78, 128.96, 129.63, 130.05, 132.33, 132.39, 132.81, 134.00, 134.02, 134.06, 134.19, 138.87, 139.44, 147.62 ppm; HRMS: *m/z* calcd. for $C_{26}H_{35}ClN_3O_2SSi$: 516.1908 $[M+H]^+$, found 516.1909.

[3-({[5-Chloro-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl]methyl}oxy)propyl]dimethylamine (9v). Obtained from **8j** as a yellowish oil: Yield 87%; IR (ATR): 2949, 2859, 2815, 2765, 1582, 1460, 1248, 1077, 834, 766, 748 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 0.00 (s, 9H), 0.85–0.92 (m, 2H), 1.79 (quin, J = 6.82 Hz, 2H), 2.20 (s, 6H), 2.37 (t, J = 6.87 Hz, 2H), 3.57–3.73 (m, 4H), 4.74–4.85 (m, 2H), 5.55 (d, J = 11.29 Hz, 1H), 5.67 (d, J = 11.29 Hz, 1H), 7.50–7.62 (m, 3H), 7.69 (d, J = 8.24 Hz, 1H), 7.76–7.85 ppm (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ −1.14, 17.61, 27.63, 40.37, 45.54, 56.30, 64.85, 65.87, 68.93, 73.41, 127.59, 128.79, 128.97, 129.63, 130.07, 132.32, 132.38, 132.81, 134.00, 134.06, 134.19, 138.84, 139.43, 147.68 ppm; HRMS: *m/z* calcd. for $C_{27}H_{37}ClN_3O_2SSi$: 530.2064 $[M+H]^+$, found 530.2048.

General procedure for preparation of compounds 10. To a solution of **9** (61.6 mg, 0.132 mmol) in methanol (3.4 mL), 0.5*M* hydrochloric acid in methanol (1.15 mL) was slowly added. The reaction mixture was heated for 2 h at 60°C, then cooled to room temperature, and concentrated. Ethyl acetate (4 mL) and water were added (6 mL) and pH adjusted to 1.0 using a 3*M* hydrochloric acid. The layers were separated and the aqueous layer washed with diethyl ether (2 × 10 mL). The pH of the aqueous layer was adjusted to pH 9.5 with 5*M* sodium hydroxide and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off, and solvent was removed *in vacuo* to give the crude product **10**.

{2-[(1H-Dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-ylmethyl)oxy]ethyl}dimethylamine (10a). Obtained from **9i** as a yellowish amorphous solid: Yield 89%; IR (ATR): 3055, 2947, 2858, 2826, 2772, 1501, 1454, 1341, 1216, 1098, 1035, 743 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.17 (s, 6H), 2.48 (t, J = 5.95 Hz, 2H), 3.63 (t, J = 5.80 Hz, 2H), 4.60 (s, 2H), 7.21–7.30 (m, 2H), 7.30–7.37 (m, 4H), 7.64 (d, J = 7.32 Hz, 2H), 12.98 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.83, 58.59, 65.67, 68.49, 122.01, 125.78, 126.05, 129.30, 147.43, 154.61 ppm; HRMS: *m/z* calcd. for $C_{20}H_{22}N_3O_2$: 336.1712 $[M+H]^+$, found 336.1726.

{3-[(1H-Dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-ylmethyl)oxy]propyl}dimethylamine (10b). Obtained from **9j** as a yellowish amorphous solid: Yield 76%; IR (ATR): 3055, 2946, 2860, 2824, 2776, 1501, 1453, 1216, 1096, 1031, 760, 742 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.69 (quin, J = 6.82 Hz, 2H), 2.11 (s, 6H), 2.27 (t, J = 7.17 Hz, 2H), 3.55 (t, J = 6.56 Hz, 2H), 4.56 (s, 2H), 7.21–7.29 (m, 2H), 7.30–7.39 (m, 4H), 7.65 (d, J = 6.10 Hz, 2H), 12.91 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.66, 45.51, 56.34, 65.61, 68.70, 122.00, 125.75, 126.11, 129.31, 147.34, 154.62 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3O_2$: 350.1869 $[M+H]^+$, found 350.1854.

{2-[(1H-Dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-ylmethyl)oxy]ethyl}dimethylamine (10c). Obtained from **9k** as a yellowish amorphous solid: Yield 90%; IR (ATR): 3044, 2944, 2855, 2824, 2772, 1489, 1459, 1340, 1115, 1032, 757 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 6H), 2.49 (t, J = 6.10 Hz, 2H), 3.66 (t, J = 5.80 Hz, 2H), 4.62 (s, 2H), 7.32–7.47 (m, 4H), 7.58 (d, J = 7.63 Hz, 2H), 7.67 (d, J = 2.75 Hz, 2H), 13.02 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.81, 58.60, 65.64, 68.60, 127.69, 129.09, 129.20, 131.71, 132.87, 146.82 ppm; HRMS: *m/z* calcd. for $C_{20}H_{22}N_3OS$: 352.1484 $[M+H]^+$, found 352.1477.

{3-[(1H-Dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-ylmethyl)oxy]propyl}dimethylamine (10d). Obtained from **9l** as a yellowish amorphous solid: Yield 86%; IR (ATR): 3051, 2944, 2860, 2820, 2772, 1489, 1461, 1355, 1093, 1032, 757 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.70 (quin, J = 6.82 Hz, 2H), 2.11 (s, 6H), 2.29 (t, J = 7.32 Hz, 2H), 3.57 (t, J = 6.41 Hz, 2H), 4.59 (s, 2H), 7.33–7.47 (m, 4H), 7.58 (d, J = 7.63 Hz, 2H), 7.67 (br. s., 2H), 12.90 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.81, 58.60, 65.64, 68.60, 127.69, 129.09, 129.20, 131.71, 132.87, 146.82 ppm; HRMS: *m/z* calcd. for $C_{21}H_{24}N_3OS$: 366.1640 $[M+H]^+$, found 366.1646.

(2-{[(11-Chloro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)dimethylamine (10e). Obtained either from **9m** (yield 90%) or **9r** (yield 83%) as a yellowish amorphous solid: IR (ATR): 3059, 2946, 2858, 2825, 2772, 1601, 1497, 1444, 1220, 1101, 836, 768, 742 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 6H), 2.48 (t, J = 5.95 Hz, 2H), 3.63 (t, J = 5.80 Hz, 2H), 4.60 (s, 2H), 7.25–7.32 (m, 1H), 7.34–7.41 (m, 4H), 7.61–7.68 (m, 2H), 13.00 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.82, 58.58, 65.64, 68.54, 122.09, 123.83, 125.28, 126.07, 126.14, 128.68, 129.71, 129.84, 147.94, 153.09, 154.29 ppm; HRMS: *m/z* calcd. for $C_{20}H_{21}N_3O_2Cl$: 370.1322 $[M+H]^+$, found 370.1335.

(3-{[(11-Chloro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)dimethylamine (10f). Obtained either from **9n** (yield 89.0%) or **9s** (yield 88.0%) as a yellowish amorphous solid: IR (ATR): 3055, 2946, 2861, 2823, 2776, 1496, 1446, 1220, 1092, 835, 814, 767, 741 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.69 (quin, J = 6.82 Hz, 2H), 2.11 (s, 6H), 2.28 (t, J = 7.32 Hz, 2H), 3.55 (t, J = 6.56 Hz, 2H), 4.56 (s, 2H), 7.24–7.31 (m, 1H), 7.34–7.40 (m, 4H), 7.62–7.70 (m, 2H), 12.96 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.63, 45.50, 56.32, 65.57, 68.76, 122.08, 123.82, 125.33, 126.04, 126.21, 128.69, 129.71, 129.83, 147.87, 153.09, 154.29 ppm; HRMS: *m/z* calcd. for $C_{21}H_{23}N_3O_2Cl$: 384.1479 $[M+H]^+$, found 384.1471.

(2-{[(11-Chloro-1H-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}ethyl)dimethylamine (10g). Obtained either from **9o** (yield 90%) or **9t** (yield 91%) as a white amorphous solid: IR (ATR): 3202, 2937, 2865, 2824, 2773, 1580, 1485, 1456, 1353, 1093, 1030, 811, 766 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.18 (s, 6H), 2.50 (t, J = 6.10 Hz, 2H), 3.66 (t,

J = 5.80 Hz, 2H), 4.63 (s, 2H), 7.36–7.50 (m, 3H), 7.56–7.62 (m, 2H), 7.63–7.72 (m, 2H), 13.07 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 45.79, 58.57, 65.60, 68.64, 126.99, 127.78, 128.61, 129.48, 130.29, 131.20, 133.03, 133.95, 134.41, 147.33 ppm; HRMS: m/z calcd. for $C_{20}H_{21}N_3OSCl$: 386.1094 [M+H]$^+$, found 386.1110.

(3-{[(11-Chloro-1*H*-dibenzo[2,3:6,7]thiepino[4,5-d]imidazol-2-yl)methyl]oxy}propyl)dimethylamine (10h). Obtained either from **9p** (yield 95%) or **9v** (yield 91%) as a yellowish amorphous solid: IR (ATR): 2943, 2860, 2819, 2772, 1579, 1484, 1459, 1094, 1030, 810, 765 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.70 (quin, J = 6.82 Hz, 2H), 2.11 (s, 6H), 2.29 (t, J = 7.32 Hz, 2H), 3.58 (t, J = 6.56 Hz, 2H), 4.59 (s, 2H), 7.34–7.49 (m, 3H), 7.54–7.62 (m, 2H), 7.62–7.75 (m, 2H), 13.01 ppm (br. s., 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.65, 45.52, 56.34, 65.51, 68.85, 127.05, 127.86, 128.62, 129.46, 129.50, 130.30, 131.22, 133.02, 133.94, 134.40, 147.21 ppm; HRMS: m/z calcd. for $C_{21}H_{23}N_3OSCl$: 400.1250 [M+H]$^+$, found 400.1254.

Biology

Cell isolation. Peripheral blood mononuclear cells (PBMC) were obtained from buffy coat of healthy volunteer donors by a density gradient centrifugation. Buffy coat was mixed with one volume of sterile saline, sample layered over FicollPaqueTM Plus (Amersham Biosciences), and centrifuged at 400 × g for 30 min. PBMCs were collected, washed in RPMI 1640 medium, and centrifuged. Finally, cells were resuspended in RPMI 1640 containing 10% heat inactivated fetal bovine serum (Biowest) and counted.

Cell culture. PBMCs were cultured at a concentration of 3.5 × 104 in 200 μL volumes in 96-well cell culture plates (Falcon, St. Albans, UK) at 37°C in humidified atmosphere containing 5% CO_2. The cells were either stimulated with LPS (serotype 0111:B4, Sigma) at 1 ng/mL final concentration or left unstimulated (cultured in medium alone). Compound stock solutions were prepared as 10 mM in DMSO. Final 10 μM and 3 μM (10–0.03 μM) concentration made in cell culture medium were tested when they had been added together with LPS. The final DMSO volume ratio in all assays did not exceed 0.1%. Negative and LPS control samples were prepared in sextaplicates and tested compound samples in triplicates.

Cytokine measurement. Cell free supernatants were taken after overnight period and quantified for TNF-α content by enzyme linked immunosorbent assay (ELISA). To ensure the detection specificity and sensitivity, assay was performed according to manufacturer instructions (R&D Systems) using suggested pair of antibodies specific for human TNF-α. Test sensitivity for measuring human TNF-α was under 5 pg/mL. To calculate results, standard curve was made out of measured OD values for recombinant TNF-α of known concentrations. TNF-α content in unknown samples was calculated out of OD values extrapolated from the standard curve. Inhibition values were calculated according to formula:

$$X = \frac{\text{Conc(compound)} - \text{Conc(medium control)}}{\text{Conc(LPS control)} - \text{Conc (medium control)}} \times 100(\%)$$

IC50 values are calculated using GraphPad Prism software.

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