Synthesis of Substituted 4-(5-Alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-Dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine

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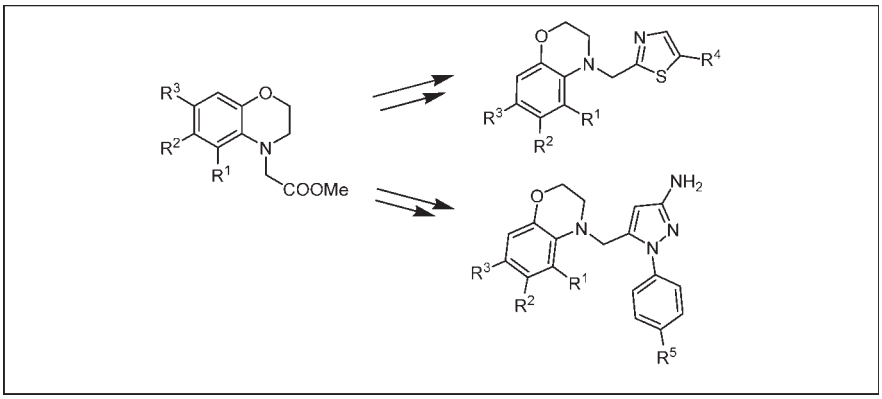

Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamines were prepared by the reaction of (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester and some common reagents to provide the product in satisfactory yields.

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INTRODUCTION

Benzoxazines have been used as intermediates in the synthesis of many heterocyclic structures of biological importance. These derivatives have been shown to be selective serotonin reuptake inhibitors. They have also shown activities toward 5-HT_{1A} receptor while the 1,4-benzoxazine imidazole derivatives have shown *in vivo* activities against a murine experimental model of candidiasis. Some of the benzoxazines were most effective in promoting HUVEC apoptosis and inhibiting A549 cell proliferation [1–4]. Some of the *N*-substituted benzoxazines have been reported to cure thrombi-related diseases, for instance, platelet aggregation, thrombosis, myocardial infarction [5] *etc*. Derivatives of benzomorpholine have been incorporated to show hypotensive/antihypertensive effectiveness [6] as well as potential dopamine D_3 receptor ligands and inhibitions of cardiac phosphodiestrase (PDE) fraction *in vitro* and for positive inotropic activity *in vivo* [7]. They also tend to inhibit oxidative stress mediated neuronal degeneration in neuronal cell cultures [8,9].

The pyrazole and thiazole ring systems are common structural motifs in a number of biologically active molecules. Thiazole ring systems originate in nature as a consequence of peptide modification containing cysteine side chain residue and are the product of cyclodehydration and redox reactions. More recently, extensive studies have been focused on aryl pyrazoles for exhibiting cyclooxygenase-2 (COX-2) and non-nucleoside HIV-1 reverse transcriptase inhibitory properties. This structure has found applications in drug development for the treatment of allergies, hypertension, schizophrenia, inflammation, bacterial, and HIV7 infections. Aminothiazoles are known to be ligands of estrogen receptors as well as a novel class of adenosine receptor antagonists, whereas other analogues are used as fungicides, inhibiting *in vivo* growth of *Xanthomonas* and as an ingredient of herbicides or as schistosomicidal and antihelmintic drugs [10–15].

RESULTS AND DISCUSSION

As part of an ongoing program aimed at synthesizing benzoxazine derivatives of biological interest, we wanted to introduce different heterocyclic ring systems on the *N*-atom of the benzoxazines. Our literature survey revealed that benzoxazines-bearing pyrazole and thiazole rings on the *N*-atom have not been reported in spite of the fact that these two heterocyclic systems played an important role in drug development.

Earlier, we have reported [16] the synthesis of 3,4-dihydro-1,4-2*H*-benzoxazine from 2-aminophenols and

Table 1

Preparation of *N*-substituted 3,4-dihydro-2*H*-1,4-benzoxazines.

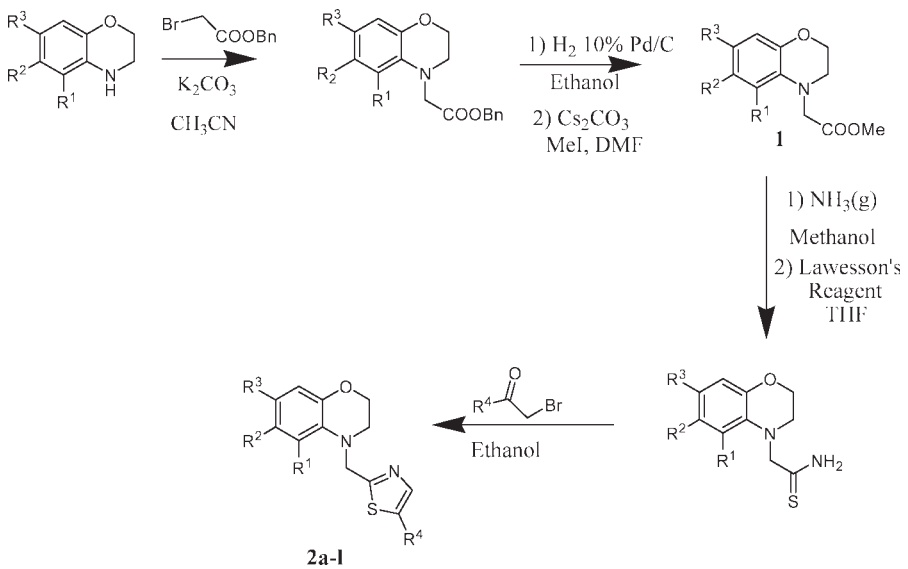
Entry	Product (**2a–j**)	Yield **2a–j** (%)	Product (**3a–j**)	Yield **3a–j** (%)
a	$R^1 = H, R^2 = H, R^3 = H\ R^4 = Me$	64	$R^1 = H, R^2 = H, R^3 = H, R^5 = H$	59
b	$R^1 = H, R^2 = H, R^3 = H\ R^4 = CH_2CH_3$	61	$R^1 = H, R^2 = H, R^3 = H, R^5 = Me$	57
c	$R^1 = H, R^2 = H, R^3 = Me, R^4 = Me$	53	$R^1 = Me, R^2 = H, R^3 = H, R^5 = H$	59
d	$R^1 = H, R^2 = H, R^3 = Me, R^4 = CH_2CH_3$	54	$R^1 = H, R^2 = Me, R^3 = H, R^5 = H$	61
e	$R^1 = H, R^2 = Me, R^3 = H, R^4 = CH_2CH_3$	61	$R^1 = H, R^2 = F, R^3 = H, R^5 = H$	62
f	$R^1 = Me, R^2 = H, R^3 = H, R^4 = CH_2CH_3$	57	$R^1 = H, R^2 = CF_3, R^3 = H, R^5 = H$	45
g	$R^1 = H, R^2 = H, R^3 = H, R^4 = Ph$	58	$R^1 = H, R^2 = Cl, R^3 = H, R^5 = Me$	41
h	$R^1 = H, R^2 = H, R^3 = Me\ R^4 = Ph$	59	$R^1 = H, R^2 = Me, R^3 = H, R^5 = Me$	47
i	$R^1 = H, R^2 = Me, R^3 = H\ R^4 = Ph$	62	$R^1 = H, R^2 = F, R^3 = H, R^5 = Me$	46
j	$R^1 = Me, R^2 = H, R^3 = H\ R^4 = Ph$	62	$R^1 = H, R^2 = H, R^3 = Me, R^5 = H$	61

1,2-dibromoethane using K_2CO_3 in DMF, which was then subjected to *N*-substitution using alkyl bromide. Subsequent debenzylation and esterification yielded (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester **1**. Here, we report the synthesis of 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazines and 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine starting from (2,3-dihydro-1,4-benzoxazin-4-yl)-acetic acid methyl ester.

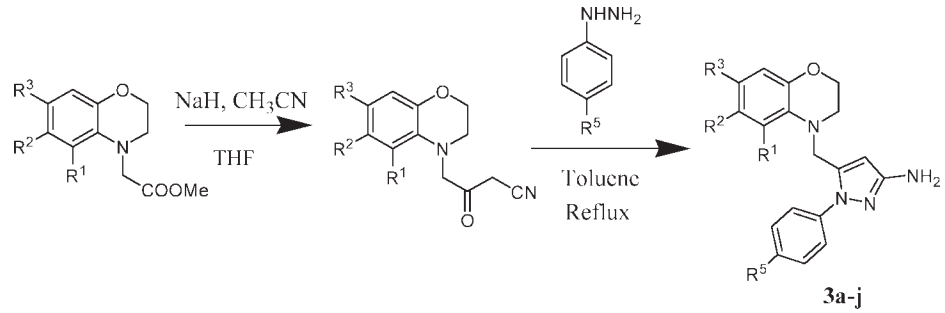
The compounds **2a–j** (Table 1) were first prepared by converting the methyl ester derivatives to amide derivatives by passing NH_3 (g) through the solution of **3** at 0–5°C and then to the corresponding thioamides using Lawesson's reagent (Scheme 1). Further treatment with 1-bromo-alkan-2-one in ethanol gave the desired products in about 53–64% yields.

Compounds **3a–j** (Table 1) was prepared by first converting the methyl ester derivatives to the corresponding butyronitrile derivatives using NaH and acetonitrile. Further treatment with phenyl hydrazine yielded the desired products in 41–62% yields (Scheme 2). Catalytic amounts of KF increased the rate of the reaction and hence the yield.

Scheme 1



Scheme 2



EXPERIMENTAL

Carbon, hydrogen, and nitrogen analysis were performed with a Perkin-Elmer 2400 series II instrument. IR spectra were recorded on a BOMEM DA-8 FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics).

Synthesis of Substituted 4-(5-alkyl-thiazol-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazine. The methyl ester derivative (**1**) was first dissolved in methanol, the reaction mixture was cooled in ice, and NH_3 gas was passed through it for 10 min. The reaction mixture was stirred overnight at room temperature, resulting in separation of dirty white solids, which were separated by filtration to yield the amide derivative. The crude product was washed with hexane to yield the pure product. IR (KBr) ν cm^{-1} 3330 (m) and 3050 (m) ($CONH_2$) H^1 NMR (DMSO-d_6, 400 MHz) δ ppm 3.3 (t, 2H, J = 14.1 Hz), 4.07 (s, 2H,), 4.32 (t, 2H, J = 9.1 Hz), 6.24 (b, 2H), 6.46–6.5 (m, 4H). Calc. for $C_{10}H_{12}N_2O_2$ C, 62.49; H, 6.29; N, 14.57%; observed were C, 62.50; H, 6.28; N, 14.56%.

The amide derivative was then dissolved in Dry THF and treated with Lawesson's reagent (0.5 eq) and stirred overnight under N_2 atm. The reaction on completion was evaporated in vacuum and extracted with ethylacetate. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:10) as an eluent to yield the desired product. IR (KBr) ν cm^{-1} 1175. The 2-(2,3-dihydro-1,4-benzoxazin-4-yl)-thioacetamide was then refluxed with 1-bromo butan-2-one in ethanol, the reaction was monitored using TLC. The reaction on completion was evaporated in vacuum and extracted with DCM. The complete organic extract was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane (1:20) as an eluent to yield the desired product (**2b**). IR (KBr) ν cm^{-1} 1725 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.17 (t, 3H, J = 14.2 Hz), 3.3–3.31 (q, 2H, J = 8.6 Hz), 3.82 (t, 2H, J = 14.3 Hz), 4.27 (t, 2H, J = 8.9 Hz), 5.72 (s, 2H), 6.46–6.65 (m, 4H), 7.04 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.6, 22.8, 57.6, 60.2 (NCH_2), 73.1 (OCH_2), 112.8, 116.8, 117.3, 119.5, 130.2, 133.4, 140.1, 141.3, 166.1, m/z = 261.26. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.18; N, 10.75%.

(**2a**). IR (KBr) ν cm^{-1} 1720 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.37 (s, 3H), 3.81 (t, 2H, J = 14.3 Hz), 4.22 (t, 2H, J = 8.9 Hz), 4.72 (s, 2H), 6.46–6.65 (m, 4H, ArH), 7.23 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.2, 58.6, 60.2 (NCH_2), 73.1 (OCH_2), 113.8, 115.8, 118.3, 120.5, 130.6, 133.7, 140.1, 143.3, 165.4, m/z = 247.26. Calc. for $C_{13}H_{14}N_2OS$ C, 63.39; H, 5.73; N, 11.37%; observed were C, 63.41; H, 5.75; N, 11.36%.

(**2c**). IR (KBr) ν cm^{-1} 1722 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.32 (s, 3H), 2.47 (s, 3H), 3.84 (t, 2H, J = 12.3 Hz), 4.22 (t, 2H, J = 9.1 Hz), 4.76 (s, 2H), 6.46–6.65 (m, 3H, ArH), 7.31 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5, 115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0, m/z = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.20; N, 10.75%.

(**2d**). IR (KBr) ν cm^{-1} 1721 (C—N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.18 (t, 3H, J = 14.1 Hz), 2.31 (s, 3H), 3.29–3.39 (q, 2H, J = 8.7 Hz), 3.82 (t, 2H, J = 14.3 Hz), 4.27 (t, 2H, J = 14.1 Hz), 5.69 (s, 2H), 6.41(s, 1H), 6.38 (d, 1H, J = 7.2 Hz), 6.47 (d, 1H, J = 7.2 Hz), 7.11 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 21.9, 22.7, 57.7, 60.1 (NCH_2), 73.3 (OCH_2), 112.8, 113.3, 119.9, 127.1, 130.4, 133.5, 140.2, 141.4, 166.1, m/z = 274.26. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21%; observed were C, 65.64; H, 6.60; N, 10.22%.

(**2e**). IR (KBr) ν cm^{-1} 1718 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 1.15 (t, 3H, J = 14 Hz), 3.29–3.33 (q, 2H, J = 8.7 Hz), 3.80 (t, 2H, J = 14.2 Hz), 4.26 (t, 2H, J = 14 Hz), 5.69 (s, 2H), 6.51–6.60 (m, 4H), 7.15 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.7, 22.9, 57.4, 60.2 (NCH_2), 73.4 (OCH_2), 113.1, 114.3, 118.9, 120.5, 130.9, 133.9, 140.6, 141.9, 166.3, m/z = 261.10. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.60; H, 6.18; N, 10.74%.

(**2f**). IR (KBr) ν cm^{-1} 1719 (C=N stretching) H^1 NMR ($CDCl_3$, 100 MHz) δ ppm 1.15 (t, 3H, J = 14.1 Hz), 2.30 (s, 3H), 3.34–3.39 (q, 2H, J = 8.9 Hz), 3.84 (t, 2H, J = 14.2 Hz), 4.29 (t, 2H, J = 14.0 Hz), 5.70 (s, 2H), 6.41–6.47 (m, 3H), 7.16 (s, 1H). C^{13} NMR ($CDCl_3$, 400 MHz) δ ppm 15.5, 16.9, 22.5, 57.5, 60.2 (NCH_2), 73.6 (OCH_2), 112.8, 119.9, 120.7, 127.1, 130.4, 130.9, 133.5, 141.4, 165.8, m/z = 275.12. Calc. for $C_{15}H_{18}N_2OS$ C, 65.66; H, 6.61; N, 10.21%; observed were C, 65.64; H, 6.62; N, 10.20%.

(**2g**). IR (KBr) ν cm^{-1} 1720 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 3.84 (t, 2H, J = 14.0 Hz), 4.20 (t, 2H, J = 9.0 Hz), 4.76 (s, 2H), 6.46–6.65 (m, 4H, ArH), 7.23–7.32 (m, 5H, ArH), 8.21 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 14.5, 21.7, 58.4, 60.2 (NCH_2), 74.1 (OCH_2), 113.5,

115.9, 121.5, 127.1, 127.8, 133.7, 140.1, 143.3, 165.0, *m/z* = 247. Calc. for $C_{14}H_{16}N_2OS$ C, 64.58; H, 6.19; N, 10.76%; observed were C, 64.61; H, 6.21; N, 10.75%.

(**2i**). IR (KBr) ν cm^{-1} 31722 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.34 (s, 3H), 3.80 (t, 2H, *J* = 14 Hz), 4.32 (t, 2H, *J* = 14.1 Hz), 5.76 (s, 2H), 6.33 (s, 1H), 6.39 (d, 1H, *J* = 7.8 Hz), 6.47 (d, 1H, *J* = 7.8 Hz), 7.39–7.45 (m, 5H), 7.89 (s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 114.9, 118.7, 126.1, 128.2, 129.1, 130.3, 135.7, 133.5, 141.4, 142.8, 147.3, 166.8, *m/z* = 322.11. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69%; observed were C, 70.77; H, 5.61; N, 8.68%.

(**2j**). IR (KBr) ν cm^{-1} 1715 (C=N stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 2.31 (s, 3H), 3.82 (t, 2H, *J* = 14 Hz), 4.31 (t, 2H, *J* = 14.1 Hz), 5.79 (s, 2H), 6.43–6.49 (m, 3H), 7.36–7.42 (m, 5H), 7.91(s, 1H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 15.5, 57.9, 60.7 (NCH_2), 73.9 (OCH_2), 112.8, 119.9, 120.7, 126.1, 127.1, 128.2, 129.1, 130.9, 135.4, 133.5, 141.4, 147.3, 166.8, *m/z* = 322.12. Calc. for $C_{19}H_{18}N_2OS$ C, 70.78; H, 5.63; N, 8.69%; observed were C, 70.76; H, 5.62; N, 8.70%.

Synthesis of 5-(2,3-dihydro-1,4-benzoxazin-4-ylmethyl)-4-methyl-1-phenyl-1*H*-pyrazol-3-ylamine. It involves the synthesis of butyronitrile derivative from the methyl ester(**1**) using acetonitrile (1.5 eq) and NaH (1.5 eq) in THF under N_2 atmosphere. The NaH was dissolved in THF, and acetonitrile was added drop wise at 0°C. The reaction mixture was allowed to stir at room temperature for ½ h and followed by drop wise addition of (**1**) solution in THF at 0°C. The reaction was then stirred at room temperature for 3 h. On completion of the reaction, the solvent was evaporated and work-up using ethyl acetate, the complete organic extracts were dried over Na_2SO_4 and evaporated to yield the crude product, which was purified by column chromatography using ethyl acetate and hexane (1:20). IR (KBr) ν cm^{-1} 2242 (CN stretching) H^1 NMR ($CDCl_3$, 400 MHz) δ ppm 3.61 (s, 2H), 3.82–3.86 (m, 2H), 4.24–4.26 (m, 2H), 4.56(s, 2H), 6.5–6.84 (m, 4H). Calc. for $C_{12}H_{12}N_2O_2$ C, 66.65; H, 5.59; N, 12.96%; observed were C, 66.64; H, 5.60; N, 12.94%. The butyronitrile derivative was then refluxed with substituted phenyl hydrazine (1.2 eq) for 4–5 h. The reaction on completion was evaporated under vacuum and worked-up using DCM. The complete organic was dried over Na_2SO_4 and evaporated to yield the crude product, which was purified by column chromatography using methanol and DCM (1:50) as an eluent.

(**3a**). IR (KBr) ν cm^{-1} 3420 (NH_2 stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 3.84–3.86 (t, 2H, *J* = 14 Hz), 4.25–4.27 (t, 2H, *J* = 8.9 Hz), 5.56 (s, 2H), 6.4–6.84 (m, 4H) 7.3–7.5 (m, 5H) 7.9 (s, 1H) 8.2 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 50.1, 60.2 (NCH_2), 73.1 (OCH_2), 94.8, 112.8, 116.8, 117.3, 118.8, 119.5, 126.5, 129.1, 130.2, 135.6, 139.8, 141.1, 164.3. *m/z* = 307. Calc. for $C_{18}H_{18}N_4O$ C, 70.57; H, 5.92; N, 18.29%; observed were C, 70.59; H, 5.91; N, 18.3%.

(**3b**). IR (KBr) ν cm^{-1} 3412 (NH_2 stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.36 (s, 3H), 3.86 (t, 2H, *J* = 14 Hz), 4.27 (t, 2H, *J* = 8.9 Hz), 5.42 (s, 2H), 6.35 (s, 1H), 6.48–6.64 (m, 4H) 7.35–7.51 (m, 4H, ArH), 8.12 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 21.2, 50.2, 59.2 (NCH_2), 74.1 (OCH_2), 94.8, 113.8, 115.8, 117.9, 118.3, 121.5, 129.5, 130.8, 135.2, 136.1, 136.9, 143.1, 164.1. *m/z* = 321. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.25; H, 6.31; N, 17.51%.

(**3c**). IR (KBr) ν cm^{-1} 3412 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.42 (s, 3H), 3.81 (t, 2H, *J* = 9.8 Hz), 4.20 (t, 2H, *J* = 9.0 Hz), 5.22 (s, 2H), 6.31 (s, 1H), 6.40–6.44 (m, 3H) 7.31–7.45 (m, 5H, ArH), 7.02 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 13.2, 50.4, 59.6 (NCH_2), 73.9 (OCH_2), 94.9, 112.8, 118.0, 118.6, 121.8, 126.2, 129.2, 131.1, 136.1, 136.9, 139.9, 143.1, 163.8. *m/z* = 319. Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.24; H, 6.30; N, 17.48%.

(**3d**). IR (KBr) ν cm^{-1} 3421 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.47 (s, 3H), 3.85 (t, 2H, *J* = 9.5 Hz), 4.23 (t, 2H, *J* = 9.1 Hz), 5.27 (s, 2H), 6.39 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, *J* = 7.2 Hz), 6.52 (d, 1H, *J* = 7.2 Hz), 7.31–7.45 (m, 5H, ArH), 7.06 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.2, 32.3, 59.3 (NCH_2), 74.1 (OCH_2), 92.9, 113.8, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. *m/z* = 320.16 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29; N, 17.49%; observed were C, 71.22; H, 6.30; N, 17.47%.

(**3e**). IR (KBr) ν cm^{-1} 3420 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.82 (t, 2H, *J* = 9.5 Hz), 4.21 (t, 2H, *J* = 9.1 Hz), 5.25 (s, 2H), 6.38 (s, 1H), 6.40 (s, 1H), 6.44 (d, 1H, *J* = 7.1 Hz), 6.50 (d, 1H, *J* = 7.1 Hz), 7.33–7.45 (m, 5H, ArH), 7.03 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 32.9, 59.4 (NCH_2), 74.2 (OCH_2), 92.9, 103.7, 105.8, 116.1, 118.6, 126.2, 129.2, 136.1, 137.9, 138.9, 146.1, 154.1, 160.8. *m/z* = 324.16 Calc. for $C_{18}H_{17}FN_4O$ C, 66.65; H, 5.28; N, 17.27%; observed were C, 66.63; H, 5.30; N, 17.26%.

(**3f**). IR (KBr) ν cm^{-1} 3427 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 3.86 (t, 2H, *J* = 9.1 Hz), 4.24 (t, 2H, *J* = 9.2 Hz), 5.28 (s, 2H), 6.41 (s, 1H), 6.74 (s, 1H), 6.79 (d, 1H, *J* = 7.0 Hz), 6.85 (d, 1H, *J* = 7.0 Hz), 7.36–7.45 (m, 5H, ArH), 7.23 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 33.1, 59.5 (NCH_2), 74.4 (OCH_2), 93.2, 110.5, 115.1, 116.0, 120.8, 124.1, 125.9, 129.2, 136.1, 137.9, 138.9, 144.1, 146.1, 160.8. *m/z* = 374.26 Calc. for $C_{19}H_{17}F_3N_4O$ C, 60.96; H, 4.58; N, 14.97%; observed were C, 60.97; H, 4.60; N, 14.96%.

(**3g**). IR (KBr) ν cm^{-1} 3439 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 3.85 (t, 2H, *J* = 9.0 Hz), 4.21 (t, 2H, *J* = 9.1 Hz), 5.30 (s, 2H), 6.39 (s, 1H), 6.54 (s, 1H), 6.69 (d, 1H, *J* = 7.2 Hz), 6.75 (d, 1H, *J* = 7.2 Hz), 7.45 (d, 2H, *J* = 7.1 Hz), 7.48 (d, 2H, *J* = 7.1 Hz), 7.18 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8 (NCH_2), 74.1 (OCH_2), 93.7, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 144.1, 145.2, 160.8. *m/z* = 354.16 Calc. for $C_{19}H_{19}ClN_4O$ C, 64.31; H, 5.40; N, 15.79%; observed were C, 64.30; H, 5.41; N, 15.80%.

(**3h**). IR (KBr) ν cm^{-1} 3424 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.31 (s, 3H), 2.35 (s, 3H), 3.80 (t, 2H, *J* = 9.0 Hz), 4.23 (t, 2H, *J* = 9.0 Hz), 5.31 (s, 2H), 6.35 (s, 1H), 6.44 (s, 1H), 6.51 (d, 1H, *J* = 7.1 Hz), 6.59 (d, 1H, *J* = 7.1 Hz), 7.42 (d, 2H, *J* = 7.0 Hz), 7.49 (d, 2H, *J* = 7.0 Hz), 7.21 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.1, 33.5, 59.8 (NCH_2), 74.1 (OCH_2), 93.7, 114.5, 115.5, 119.7, 120.8, 129.2, 130.3, 136.1, 137.2, 139.1, 144.1, 145.1, 160.8. *m/z* = 335.16 Calc. for $C_{20}H_{22}N_4O$ C, 71.83; H, 6.63; N, 16.75%; observed were C, 71.82; H, 6.62; N, 16.77%.

(**3i**). IR (KBr) ν cm^{-1} 3429 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.32 (s, 3H), 3.82 (t, 2H, J = 9.0 Hz), 4.24 (t, 2H, J = 9.0 Hz), 5.32 (s, 2H), 6.41 (s, 1H), 6.56 (s, 1H), 6.70 (d, 1H, J = 7.0 Hz), 6.75 (d, 1H, J = 7.0 Hz), 7.45 (d, 2H, J = 7.1 Hz), 7.48 (d, 2H, J = 7.1 Hz), 7.23 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 24.3, 33.7, 59.9 (NCH_2), 74.5 (OCH_2), 93.4, 115.1, 116.0, 119.2, 120.8, 125.9, 129.2, 136.1, 137.2, 139.9, 145.1, 144.1, 160.8. m/z = 339.16 Calc. for $C_{19}H_{19}FN_4O$ C, 67.44; H, 5.66; F, 5.61; N, 16.56%; observed were C, 67.43; H, 5.60; N, 16.58%.

(**3j**). IR (KBr) ν cm^{-1} 3422 (NH stretching) H^1 NMR (DMSO-d_6, 400 MHz), δ ppm 2.45 (s, 3H), 3.85 (t, 2H, J = 9.0 Hz), 4.28 (t, 2H, J = 9.1 Hz), 5.32 (s, 2H), 6.37 (s, 1H), 6.41 (s, 1H), 6.47 (d, 1H, J = 7.1 Hz), 6.52 (d, 1H, J = 7.1 Hz), 7.36–7.45 (m, 5H, ArH), 7.16 (b, 2H). C^{13} NMR ($CDCl_3$, 100 MHz) δ ppm 23.6, 32.6, 59.5 (NCH_2), 74.3 (OCH_2), 92.5, 113.9, 114.5, 115.1, 118.6, 126.2, 129.2, 130.1, 136.1, 137.9, 139.9, 143.1, 160.8. m/z = 321.21 Calc. for $C_{19}H_{20}N_4O$ C, 71.23; H, 6.29%; N, 17.49; observed were C, 71.22; H, 6.30; N, 17.47%.

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