Synthesis of Some Heterocyclic Imides and Azomethine Derivatives Under Solvent Free Condition and Their Anti-Inflammatory Activity Evaluation

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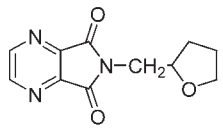

8e

31.0 % Anti-inflammatory activity at 50 mg/kg p.o.

Condensation of various mono amines with various diacids gave heterocyclic imide derivatives and condensation of amines with various aldehydes gave azomethine derivatives in good yields under solvent free condition. Structures assigned to imide and azomethine derivatives are fully supported by spectral data. All these compounds were screened for anti-inflammatory activity at a dose of 50 mg/kg p.o. Compound **8a** (6-((tetrahydrofuran-2-yl)methyl)-6H-pyrrolo[3,4]pyrazine-5,7-dione) exhibited anti-inflammatory activity comparable to standard drug phenyl butazone which showed 37% activity at 50 mg/kg p.o.

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INTRODUCTION

Increasing interest to synthesize small molecules as the structural building block is driving the development of new technologies under green chemistry research that can produce highly pure compounds at very high rate in very less time. Imides and azomethine derivatives are well known compounds as the productive component in various reactions [1]. Imides form structural part of various important natural and synthetic molecules such as fumaramidmycin [2], coniothyromycin [3], and SB-253514 [4], thalidomide [5], granulatimide [6], and isogranulatimide [7]. Wide range of biological activities, *i.e.*, anti-inflammatory [8], anticancer [9], and insecticidal [10] are shown by imide derivatives. Azomethine derivatives also possess anti-inflammatory [11], anticancer [12], antibacterial [13], and antimicrobial [14] activities.

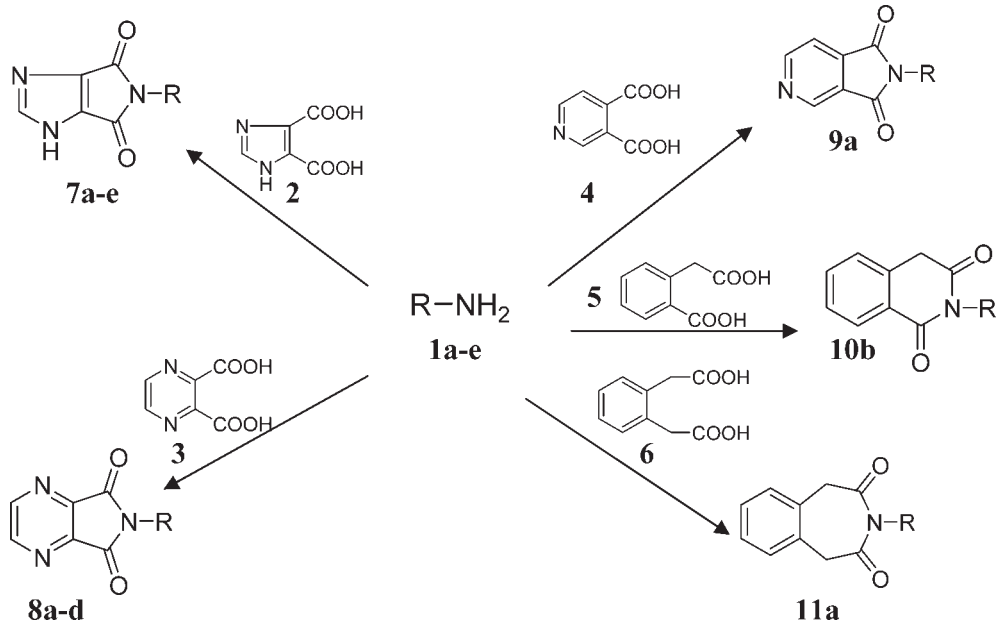
Microwave chemistry is relatively new technology that has been reported to significantly improve productivity in generation of complex target molecules. Some important features of microwave irradiation, *i.e.*, solvent free reactions, low waste, energy efficiency, high yield, and short reaction time make this technique an important tool for organic synthetic chemistry. Use of microwave chemistry and solvent free reaction conditions allow us to synthesize a large number of compounds in a very short period of time. With this hypothesis and in continuation of our work [15] in search of potent molecules exhibiting the anti-inflammatory activity, we have synthesized a number of heterocyclic imide and azomethine derivatives and screened them for anti-inflammatory activity, which we wish to report in this article.

RESULTS AND DISCUSSION

Chemistry. A number of heterocyclic imide derivatives **7a–e**, **8a–d**, **9a, 10b** and **11a** (Scheme 1) have been synthesized *via* the condensation of various amines (**1a–e**; Scheme 1) with various diacids (**2–6;** Scheme 1) under microwave irradiation conditions (power 600 Watt). Microwave irradiation of a mixture of tetrahydrofurfuryl amine (**1a**) and 4,5-imidazoledicarboxlic acid (1:1 molar ratio) at 600W for 4 min gave product **7a**. For compound **7a**, IR absorption band at 1728 cm^{-1} indicates the presence of —CO—N—CO— group. Spectral data of **7a** reported in experimental section fully support the structure assigned to it. Irradiation time and percentage yield of **7b–e**, **8a–d**, **9a**, **10b**, and **11a** synthesized by following above method is reported in Table 1.

A number of heterocyclic azomethine derivatives **15a–c** and **16a–c** have been synthesized *via* the condensation of **12**, **1c** and **1d** amines with aromatic aldehydes **13** and **14** by following reaction Scheme 2.

Scheme 1. Synthesis of heterocyclic imide derivatives.



Condensation of thiophen-2-ylmethanamine (**12**) with 2-hydroxy-1-naphthaldehyde (**13**) by irradiating at 600W for 1 min gave product **15a** in 99% yield.

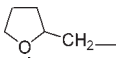
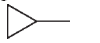
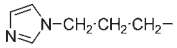
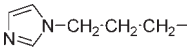
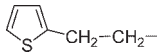
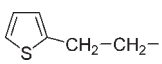
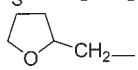
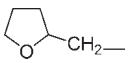
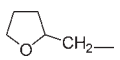
Spectral data of **15a** reported in experimental section of this article fully support the structure assigned to it. By following above method other azomethine derivatives, *i.e.*, **15b–c** and **16a–c** have been synthesized. Power level, Irradiation time and percentage yield of all the azomethine derivatives synthesized is reported in Table 2.

Conventional methods for the synthesis of imide derivatives involve refluxing of reactants in pyridine [16a], or toluene [16b], or use of PCl_3/CH_3CN [16c] etc. whereas synthesis of schiffs bases involve use of P_2O_5/Al_2O_3 [17a] as a catalyst, refluxing of reactants in toluene [17b] or ethanol [17c] or chloroform [17d] for long hours and still yields are not very good. Microwave irradiation technique [18] is reported to be an efficient way of energy transfer as compared to conventional heating and thus reduces reaction time which leads to a few side products and hence high yield of required products. In the synthesis of imide and azomethine, we used microwave irradiation technique and got desired products in high yields but in a very short period of reaction time.

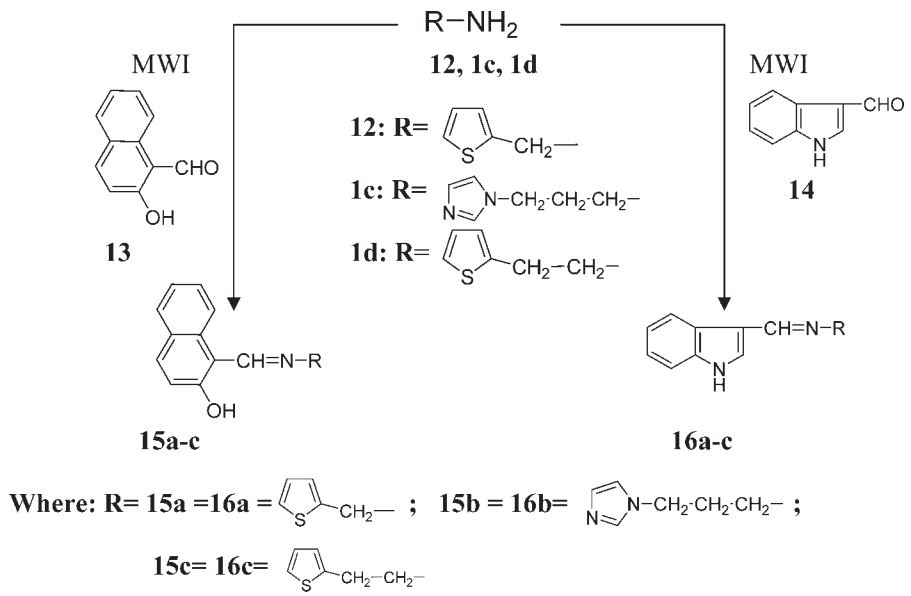
Crystal structure of compound 15a. To get the structure of compound **15a**, single crystal of compound **15a** was grown by slow evaporation of methanol solution. The quality of data for the crystal of **15a** was not very good but it was enough to predict the structure of

Table 1

Irradiation time, and percentage yield of compounds **7a–e**, **8a–d**, **9a, 10b**, **and 11a**.

Compds	R	Time (min)	% Yield	Compds	R	Time (min)	% Yield
7a		4	95	**8b**		2	90
7b		4	93	**8c**		3	86
7c		4	89	**8d**		3	85
7d		2	92	**9a**		2	98
7e		4	96	**10b**		2	96
8a		3	92	**11a**		1.5	95

Scheme 2. Synthesis of heterocyclic azomethine derivatives.



compound **15a** (Fig. 1). The crystal data of **15a** is summarized in Table 3. The crystal structure give rise to C=N bond distance of 1.301 A° which is comparable to reported value 1.282(3) A° [19].

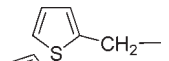
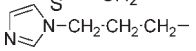
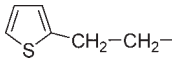
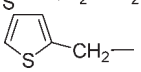
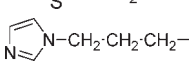
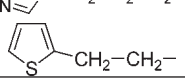
Biological activity. Anti-inflammatory [20] activity evaluation of **7a–e**, **8a–d**, **9a, 10b**, **11a, 15a–c** and **16a–c** was carried out using carrageenan-induced paw oedema model and results are summarized in Table 4. Compound **8a** exhibited 31% (50 mg/kg p.o.) where as standard drug phenyl butazone exhibited 37% (50 mg/kg p.o.) anti-inflammatory activity. Anti inflammatory activity of **8a** is comparable to phenyl butazone.

CONCLUSION

A number of heterocyclic- imide and azomethine derivatives have been synthesized in high yields in a very short time period using microwave irradiation technique. These imide and azomethine derivatives were screened for anti-inflammatory activity and compound **8a** exhibited good anti-inflammatory activity. Microwave technique is an important tool for synthetic organic chemistry.

Table 2

Power (Watt), irradiation time, and percentage yield of **15a–c** and **16a–c**.

Compd.	R	Watt	Time (min)	% yield
15a		600W	1.5	99
15b		600W	2	98
15c		600W	2	95
16a		450W	2	98
16b		450W	3	94
16c		450W	2	90

EXPERIMENTAL

General. Microwave oven model M197DL (Samsung) was used for microwave irradiation. Compounds **7a**, **8d**, and **11a** were purified by crystallization from methanol/ ethyl acetate (8:2) whereas all other compounds reported in this article were purified by crystallization from methanol. Melting points (mp) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer ^{1}H NMR spectra were recorded on a Bruker WH-500 spectrometer at a ca 5–15% (w/v) solution in DMSO-d_6 (TMS

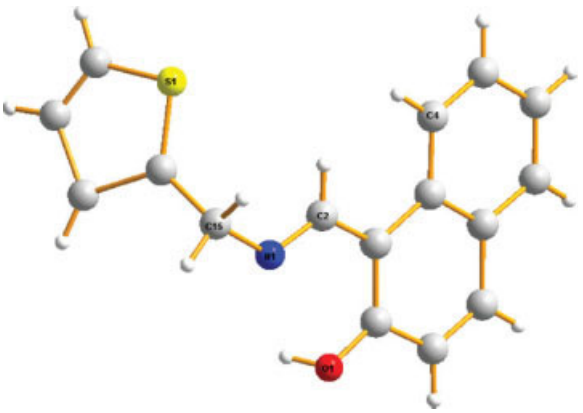


Figure 1. Crystal structure of **15a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 3

Crystal data and X-ray experimental parameters for compound **15a**.

Formula	$C_{16}H_{13}NOS$	α(deg)	90.00
Colour	White	β(deg)	108.695(2)
Crystal system	*P21/c*	γ(deg)	90.00
Space group	Monoclinic	V(A°^{3})	1293.60(7)
T(K)	273(2)	ρ_{calcd}(g cm^{-3})	2.506
a(A°)	9.8722(3)	μ(mm^{-1})	1.198
b(A°)	9.8664(3)	R1[a]	0.1899
c(A°)	14.0206(4)	wR2[b]	0.5181
Z	26	GOF[c]	4.216

[a] $R1 = \Sigma|F_o| - |F_c|/\Sigma F_o|$.
[b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.
[c] GOF $= [\Sigma[w(F_o^2 - F_c^2)^2]/M\text{-}N)]^{1/2}$ (M = number of reflections, N = number of parameters refined).

as internal standard) FAB-MS was recorded on JEOL SX-120 (FAB) spectrometer. GC-MS was recorded on Perkin Elmer Clarus 500 gas chromatograph where built in MS detector was used. Elemental analysis was carried out on a Vario EL III elementor. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (254 nm). The X-ray data collection and processing were performed on Bruker Kappa Apex-II CCD diffractometer by using graphite monochromated Mo-Kα radiation (λ = 0.71070 Å) at 100 K. Crystal structures were solved by direct methods. Structure solution, refinement and data output were carried out with the SHELXTL program [21,22]. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and refined using a riding model. Images were created with the DIAMOND program [23].

Reaction procedure for synthesis of 7a. 4,5-Imidazoledicarboxlic acid (0.200 g, 1.28 mmol) and tetrahydrofurfuryl amine (0.20 mL, 1.98 mmol) were mixed together thoroughly in a petri dish to form a paste. This paste was subjected to microwave irradiation for 4 min at a power level of 600 Watt. Completion of reaction was checked by TLC. Crude reaction product was washed with ether. The product so obtained was further purified by crystallization from ethylacetate:methanol (8:2). Yield 210mg (95%) m.p. 212°C.

Similarly were prepared compounds **7a–e**, **8a–d**, **9a, 10b** and **11a**.

Physical constant and spectral data of heterocyclic imidie derivatives **7a–e**, **8a–d**, **9a, 10b**, **11a**.

5-((Tetrahydrofuran-2-yl)methyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7a). Mp 212–214°C; IR (KBr) ν_{max}: 1728 (—CO—N—CO—), 1636, 1585, and 1462 (Ar) cm^{-1} ^{1}H NMR δ 1.20 (s, 1H, aliphatic), 1.66–1.69(d, 2H, aliphatic), 1.95–1.96 (d, 1H, aliphatic), 2.73–2.77 (t, 1H, aliphatic), 2.91–2.93 (d, 1H, aliphatic), 3.64–3.68 (q, 1H, aliphatic), 3.75–3.78 (t, 1H, CH_2), 3.98 (s, 1H, CH_2), 7.65 (s, 1H, imidazole), NH (not observed). **GC-MS** m/z 221 (M^+, 32%). Anal. Calcd. For $C_{10}H_{11}N_3O_3$ C, 54.29; H, 4.97; N, 19.00. Found C, 54.30; H, 4.93; N, 18.89.

5-Cyclopropylpyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7b). Mp 235–236°C; IR (KBr) ν_{max}: 1709 (—CO—N—CO—), 1601, 1556, and 1489 (Ar) cm^{-1} ^{1}H NMR δ 0.66–0.71 (t, 4H, —CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 7.63(s, 1H, Ar), NH (not observed). **GC-MS** m/z 177 (M^+, 20%). Anal. Calcd. For $C_8H_7N_3O_2$ C, 54.23; H, 3.95; N, 23.72. Found C, 54.23; H, 3.93; N, 23.69.

5-(3-(1H-imidazol-1-yl)propyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7c). Mp 220–221°C; IR (KBr) ν_{max}: 3399 (NH), 1670 (—CO—N—CO—), 1601 and 1556 (Ar) cm^{-1} ^{1}H NMR δ 1.94–1.99 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 4.07 (s, 2H, CH_2), 6.95 (s, 1H, Ar), 7.27 (s, 1H, Ar), 7.72 (s, 1H, Ar), 7.77 (s, 1H, Ar), 7.99 (bs, 1H, NH, exch.) **GC-MS** m/z 245 (M^+, 10%), Anal. Calcd. For $C_{11}H_{11}N_5O_2$ C, 53.87; H, 4.48; N, 28.57. Found C, 53.85; H, 4.46; N, 28.53.

5-(2-(Thiophen-2-yl)ethyl)pyrrolo[3,4-d]imidazole-4,6(1H,5H)-dione (7d). Mp 250–252°C; IR (KBr) ν_{max}: 1698 (—CO—N—CO—), 1584, 1504, and 1431 (Ar) cm^{-1} ^{1}H NMR δ 3.07–3.16 (s, 4H, 2 × CH_2), 6.97–6.99 (q, 2H, Ar), 7.41 (d, 1H, Ar), 7.56 (s, 1H, Ar), 7.84 (s, 1H, NH exch.). **GC-MS** Does not show M^+ ion peak but gave fragments at *m/z* 151($C_6H_5N_3O_2^{\bullet+}$, 9%), 150($C_6H_4N_3O_2^{\oplus}$, 7%), 137 ($C_5H_3N_3O_2^{\bullet+}$, 12%), 110 ($C_6H_6S^{\bullet+}$, 98%), 97 ($C_5H_5S^{\oplus}$, 100%). Anal. Calcd. For $C_{11}H_9N_3O_2S$ C, 53.44; H, 3.64; N, 17.00; S, 12.95. Found C, 53.40; H, 3.63; N, 17.00; S, 12.94.

5-Cyclohexylpyrrolo[3,4]imidazole-4,6-(1H,5H)-dione (7e). Mp 205–206°C; IR (KBr) ν_{max}: 1723 (—CO—N—CO—), 1589, and 1458 (Ar) cm^{-1} ^{1}H NMR δ 1.14–1.15 (m, 1H, aliphatic), 1.18–1.27 (m, 4H, aliphatic), 1.55–1.58 (m, 1H, aliphatic), 1.69 (s, 2H, aliphatic), 1.87 (s, 2H, aliphatic), 2.94 (s, 1H, aliphatic), 7.87 (s, 1H, Ar). **GC-MS** Does not show M^+ ion peak but gave fragmentation ions at *m/z* 191 ($C_{10}H_{13}N_3O^{\bullet+}$, 12%), 83 ($C_6H_{11}^{\oplus}$, 12%). Anal. Calcd. For $C_{11}H_{13}N_3O_2$ C, 60.27; H,5.93; N, 19.17. Found C, 60.25; H, 5.92; N, 19.15.

6-((Tetrahydrofuran-2-yl)methyl)-6H-pyrrolo[3,4]pyrazine-5,7-dione (8a). Mp 128–129°C; IR (KBr) ν_{max}: 1719 (—CO—N—CO—), 1585 and 1445 (Ar) cm^{-1} ^{1}H NMR δ 1.49–1.56 (m, 1H, aliphatic), 1.77–1.88 (m, 2H, aliphatic), 1.91–1.98 (m, 1H, aliphatic), 2.71–2.75 (q, 1H, aliphatic), 2.89–2.93 (dd, 1H, aliphatic), 3.64–3.68 (m, 1H, aliphatic), 3.74–3.79 (m, 1H, aliphatic), 3.95–4.00 (m, 1H, aliphatic), 8.73 (s, 2H, pyrazine). **GC-MS** m/z 233 (M^+, 20%). Anal. Calcd. For $C_{11}H_{11}N_3O_3$ C, 56.65; H, 4.72; N, 18.02. Found C, 56.64; H, 4.73; N, 18.00.

6-Cyclopropyl-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (8b). Mp 195–196°C; IR (KBr) ν_{max}: 1718 (—CO—N—CO—), 1605 and

Table 4

Anti-inflammatory activity evaluation of compounds **7a–e**, **8a–d**, **9a**, **10b**, **1 1a**, **15a–c** and **16a–c** at 50 mg /kg p.o.

Compds	Anti-inflammatory activity (%)	Compds	Anti-inflammatory activity (%)
7a	25.4	**9a**	26.1
7b	1.4	**10b**	16.0
7c	15.5	**11a**	18.3
7d	24.2	**15a**	19.7
7e	26.8	**15b**	15.6
8a	**31.0**	**15c**	0.0
8b	16.9	**16a**	27.2
8c	29.6	**16b**	10.8
8d	14.1	**16c**	0.0
		***PB**	37

* PB denote for phenyl butzone.

1421 (Ar) cm^{-1} ^1H NMR δ 0.48–0.71 (m, 4H, —CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 8.73 (s, 2H, pyrazine). **GC-MS** m/z 189 (M^+, 13%). Anal. Calcd. For $C_9H_7N_3O_2$ C,57.14; H, 3.70; N, 22.22. Found C, 57.12; H, 3.71; N, 22.20.

6-(3-(1H-imidazole-1-yl)propyl)-6H-pyrrolo-[3,4-b]pyrazine-5,7-dione (8c). Mp 189–191°C; IR (KBr) ν_{max}: 1698 (—CO—N—CO—), 1627, 1586, and 1564 (Ar) cm^{-1} ^1H NMR δ 1.98 (bs, 2H, CH_2), 2.64 (bs, 2H, CH_2), 4.06 (bs, 2H, CH_2), 6.92 (s, 1H, imidazole), 7.19 (s, 1H, imidazole), 7.66 (s, 1H, imidazole), 8.71 (s, 2H, pyrazine). **GC-MS** m/z 257 (M^+, 13%), Anal. Calcd. For $C_{12}H_{11}N_5O_2$ C, 54.30; H, 3.02; N, 12.67; S, 9.65. Found C, 54.37; H, 3.02; N, 12.65; S, 9.88.

6-(2-(Thiophene-2yl)ethyl)-6H-pyrrolo[3,4-b]pyrazine-5,7-dione (8d). Mp 136–137°C; IR (KBr) ν_{max}: 1717 (—CO—N—CO—), 1635 and 1495 (Ar) cm^{-1} ^1H NMR δ 3.03–3.09 (m, 4H, 2 × CH_2), 6.95–6.98 (q, 2H, thiophene), 7.35–7.36 (m, 1H, thiophene), 8.71 (s, 2H, pyrazine). **GC-MS** m/z 259 (M^+, 12%). Anal. Calcd. For $C_{12}H_9N_3O_2S$ C, 55.59; H, 3.47; N, 16.21; S, 12.35. Found C, 55.59; H, 3.47; N, 16.21; S, 12.35.

2-((-Tetrahydrofuran-2-yl) methyl)-2H-pyrrolo[3,4-c]pyridine-1,3dione (9a). Mp 107–108°C; IR (KBr) ν_{max}: 1715 (—CO—N—CO—), 1593, 1489, and1400 (Ar) cm^{-1} ^1H NMR δ 1.51–1.55 (q, 1H, aliphatic), 1.80–1.87 (m, 2H, aliphatic), 1.94–1.99 (m, 1H, aliphatic), 2.72–2.76 (m, 1H, aliphatic), 2.90–2.93 (m, 1H, aliphatic), 3.66–3.70 (m, 1H, aliphatic), 3.95–4.00 (m, 2H, CH_2), 7.97–7.98 (d, 1H, py), 8.73–8.74 (d, 1H, py), 9.24 (s, 1H, py). **GC-MS** m/z 232 (M^+, 21%). Anal. Calcd. For $C_{12}H_{12}N_2O_3$ C, 62.06; H, 5.17; N, 12.06. Found C, 62.05; H, 5.17; N, 12.03.

2-Cyclopropylisoquinoline-1,3-(2H,4H)-dione (10b). Mp 40–41°C; IR (KBr) ν_{max}: 1715 (—CO—N—CO—), 1629 and 1590 (Ar) cm^{-1}. ^1H NMR δ 0.63–0.68 (m, 4H, CH_2—CH_2—), one H of cyclopropyl ring merged with DMSO-d_6 signal, 3.58 (s, 2H, CH_2), 7.17–7.19 (d, 1H, Ar), 7.23–7.26 (t, 1H, Ar), 7.30–7.33 (m, 1H, Ar), 7.63–7.65 (d, 1H, Ar). **GC-MS** m/z 201 (M^+, 35%). Anal. Calcd. For $C_{12}H_{11}NO_2$ C, 71.64; H, 5.47; N, 6.96. Found C, 71.62; H, 5.44; N, 6.96.

3-(Tetrahydrofran-2-yl)methyl)-1H-benzo[d]azepine-2,4(3H,5H)-dione (11a). Mp150–151°C; IR (KBr) ν_{max}: 1711 (—CO—N—CO—), 1634, 1582, and 1491 (Ar) cm^{-1}. ^1H NMR δ 1.51–1.56 (m, 1H, aliphatic), 1.81–1.86(m, 2H, aliphatic), 1.93–1.96 (q, 1H, aliphatic), 2.68–2.73 (q, 1H, aliphatic), 2.84–2.87 (dd, 1H, aliphatic), 2.30 (s, 4H, 2 × CH_2,) 3.76–3.80 (m, 2H, aliphatic), 3.94–3.97 (q, 1H, aliphatic), 7.14–7.19 (m, 4H, Ar). **GC-MS** m/z 259 (M^+, 2%), Anal. Calcd. For $C_{15}H_{17}NO_3$ C, 69.49; H, 6.56; N, 5.40. Found C, 69.47; H, 5.56; N, 5.38.

Reaction procedure for synthesis of 15a. 2-Hydroxy-1-naphthaldehyde (0.200 g, 1.16 mmol) and thiophen-2-ylmethanamine (0.20 mL, 1.76 mmol) were mixed together thoroughly in a petri dish to form a paste. This paste was subjected to microwave irradiation for 1.5 min at power level of 600 Watt.. Completion of reaction was checked by TLC. Crude reaction product was washed with chilled ethyl acetate. The product so obtained was further purified by crystallization from Methanol. Yield 265mg (99%) m.p. 135°C.

Similarly compounds **15a–c, 16a,b** and 1**6c** were prepared. Physical constants and spectral data is reported as below.

1-((Thiophen-2-ylmethylimino)methyl)naphthalen-2-ol (15a). Mp 135–137°C; IR (KBr) ν_{max}: 3439 (OH), 1628 (C=N), 1544 and 1493 (Ar) cm^{-1}. ^1H NMR δ 5.08 (s, 2H, CH_2), 6.78–6.79 (d, 1H, Ar), 7.05–7.07 (q, 1H, Ar), 7.17–7.18 (q, 1H, Ar), 7.23–7.26 (m, 1H, Ar), 7.46–7.49 (m, 1H, Ar), 7.52–7.53 (q, 1H, Ar), 7.68–7.69 (q, 1H, Ar), 7.773–7.792 (d, 1H, Ar), 8.12–8.13 (d, 1H, Ar), 9.33–9.35 (d, 1H, Ar), 14.34 (s, 1H, OH exch.). **GC-MS** m/z 267 (M^+, 58%), Anal. Calcd. For $C_{16}H_{13}NSO$ C, 71.91; H, 4.87; N, 5.24; S, 11.98. Found C, 71.89; H, 4.86; N, 5.24; S, 11.96.

1-((3-(1H-imidazol-1-yl)propylimino)methyl)naphthalen-2-ol (15b). Mp 95–96°C; IR (KBr) ν_{max}: 3428 (OH), 1631 (C=N), 1542, 1523, and 1445 (Ar) cm^{-1}. ^1H NMR δ 2.14–2.19 (m, 2H, CH_2), 3.60–3.64 (t, 2H, CH_2), 4.06–4.09 (t, 2H, CH_2), 6.75–6.77 (d, 1H, Ar), 6.93 (s, 1H, Ar), 7.19–7.25 (m, 2H, Ar), 7.42–7.45 (m, 1H, Ar), 7.64–7.69 (m, 2H, Ar), 7.74–7.76 (d, 1H, Ar), 8.07–8.09 (d, 1H, Ar), 9.10–9.12 (d, 1H, Ar), 14.21 (s, 1H, OH exch). **GC-MS** m/z 279 (M^+, 20%). Anal. Calcd. For $C_{17}H_{17}N_3O$ C, 73.11; H, 6.09; N, 15.05. Found C, 73.10; H, 6.02; N, 15.05.

1-((Thiophen-2-yl)ethylimino)methyl)naphthalen-2-ol (15c). Mp 115–116°C; IR (KBr) ν_{max}: 3442 (OH), 1638 (C=N), 1598 and 1543 (Ar) cm^{-1}. ^1H NMR δ 3.22–3.25 (t, 2H, CH_2), 3.90–3.92 (t, 2H, CH_2), 6.71–6.73 (d, 1H, Ar), 6.97–6.99 (q, 2H, Ar), 7.17–7.21 (m, 1H, Ar), 7.36–7.38 (dd, 1H, Ar), 7.40–7.43 (m, 1H, Ar), 7.62–7.64 (dd, 1H, Ar), 7.72–7.73 (d, 1H, Ar), 8.00–8.02 (d, 1H, Ar), 9.05–9.07 (d, 1H, Ar), 14.0 (s, 1H, OH exch.). **GC-MS** m/z 281 (M^+, 49%), Anal. Calcd. For $C_{17}H_{15}NSO$ C, 72.59; H, 5.33; N, 4.98; S, 11.38. Found C, 72.59; H, 5.34; N, 4.95; S, 11.39.

N-(1H-Indol-3-yl)methylene)(thiophen-2-yl)methanamine (16a). Semisolid; IR (KBr) ν_{max}: 3395 (NH), 1637 (C=N), 1578, 1533, and 1453 (Ar) cm^{-1}. ^1H NMR δ 4.89 (s, 2H, CH_2), 7.00–7.03 (m, 2H, Ar), 7.12–7.15 (m, 1H, Ar), 7.19–7.22 (m, 1H, Ar), 7.396–7.399 (dd, 1H, Ar), 7.41–7.47 (d, 1H, Ar), 7.83 (s, 1H, Ar), 8.29–8.30 (t, 1H, Ar), 8.58 (s, 1H, Ar), 11.60 (s, 1H, NH exch.). **GC-MS** m/z 240 (M^+, 100%). Anal. Calcd. For $C_{14}H_{12}N_2S$ C, 70.00; H, 5.00; N, 11.66; S, 13.33. Found C, 69.98; H, 5.00; N, 11.65; S, 13.30.

N-((1H-indol-3-yl)methylene)-3-(1H-imidazol-1-yl)propan-1-amine (16b). Semisolid; IR (KBr) ν_{max}: 3434 (NH), 1635 (C=N), 1601, 1512, and 1499 (Ar) cm^{-1}. ^1H NMR δ 2.04–2.09 (m, 2H, CH_2), 3.44–3.47 (t, 2H, CH_2), 4.08–4.11 (t, 2H, CH_2), 6.911–6.912 (d, 1H, CH), 7.05–7.13 (m, 1H, Ar), 7.17–7.19 (m, 1H, Ar), 7.23–7.24 (m, 1H, Ar), 7.42–7.43 (d, 1H, Ar), 7.65 (s, 1H, Ar), 7.77–7.79 (d, 1H, Ar), 8.21–8.29 (t, 1H, Ar), 8.44 (s, 1H, Ar), 11.54 (s, 1H, NH exch.). **GC-MS** m/z 252 (M^+, 39%). Anal. Calcd. For $C_{15}H_{16}N_4$ C, 71.43; H, 6.35; N, 22.22. Found C, 71.42; H, 6.34; N, 22.22.

N-(1H-Indol-3-yl)methylene)(thiophen-2-yl)ethanamine (16c). Mp 98–100°C; IR (KBr) ν_{max}: 3431(NH), 1627 (C=N), 1543 and 1443 (Ar) cm^{-1}. ^1H NMR δ 3.15–3.18 (t, 2H, CH_2), 3.75–3.77 (t, 2H, CH_2), 6.92–6.95 (m, 2H, Ar), 7.10–7.13 (m, 1H, Ar), 7.17–7.20 (m, 1H, Ar), 7.29–7.30 (m, 1H, Ar), 7.426–7.432 (d, 1H, Ar), 7.74–7.77 (d, 1H, Ar), 8.27–8.28 (d, 1H, Ar), 8.42–8.44 (d, 1H, Ar), 11.52 (s, 1H, NHexch.). **GC-MS** m/z 254 (M^+, 12%). Anal. Calcd. For $C_{15}H_{14}N_2S$ C, 70.86; H, 5.51; N, 11.02; S, 12.59. Found C, 70.85; H, 5.52; N, 11.00; S, 12.58.

Preparation of single crystal for X-ray analysis. All the crystallographic parameters are tabulated in Table 3 and selected bond distance is reported in Text. Crystals of compound **15a** were obtained from slow evaporation of methanol

solution of compound **15a**. Compound **15a** crystallized in monoclinic space group *P21/c*.

Anti-inflammatory activity [20]. Paw oedema inhibition test was used on albino rats of Charles Foster by adopting the method of Winter et al [20]. Groups of five animals of both sexes (body weight 120–160 g), excluding pregnant females, were given a dose of test compound. Thirty minute later, 0.20 mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw and the volume was measured by a water plethysmometer apparatus and then measured again 1–3 h later. The mean increase of paw volume at each interval was compared with that of control group (five rats treated with carrageenan but not with test compound) at the same intervals and percent inhibition value calculated by the formula given below.

$$\%\ \text{anti-inflammatory activity} = [1 - D_t/D_c] \times 100$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively. Compounds **7a–e**, **8a–d**, **9a**, **10**b, **1 1a**, **15a–**c, and **16a–c** were screened for anti-inflammatory activity and results are summarized in Table 4.

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