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Original article

Synthesis of amidine and amide derivatives and their evaluation for anti-inflammatory and analgesic activities

Sham M. Sondhi [a,*], Jaiveer Singh [a], Ashok Kumar [b], Hyder Jamal [c], P.P. Gupta [c]

[a] Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee 247667, Uttarakhand, India
[b] Department of Pharmacology, LLRM Medical College, Meerut 250004, Uttar Pradesh, India
[c] Department of Pharmacology, BRD Medical College, Gorakhpur 273013, Uttar Pradesh, India

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ABSTRACT

A number of amidine derivatives (**2a**–**i**) have been synthesized by condensation of 2-cyanopyridine with various 3,4-diaryl-2-imino-4-thiazolines. Various amide derivatives (**3a**–**h**) were synthesized by condensation of orotic acid and hydantoin-5-acetic acid with a number of 3,4-diaryl-2-imino-4-thiazolines using microwave irradiation. All the compounds i.e. (**2a**–**i**) and (**3a**–**h**) synthesized were characterized by spectroscopic means and elemental analysis. Compounds (**2a**–**i**) and (**3a**–**h**) at 50 mg/kg p.o. were screened for anti-inflammatory activity whereas **2a**–**d**, **f**, **g**, **i** and **3a**, **b**, **d**, **f** at 50 mg/kg p.o. were evaluated for analgesic activity. Compounds **2e** and **3g** exhibited good anti-inflammatory activity (49% and 34%, respectively) and **2f**, **g** showed interesting (50% in each case) analgesic activity.

1. Introduction

Arthritis, asthma, allergy, multiple sclerosis and other diseases which cause inflammation and pain are widely prevalent throughout the world. For the treatment of pain and inflammation various drugs such as indomethacin, ibuprofen, dichlofenac, aspirin, nimisulide, celecoxib, rofecoxib, etc. are available in the market [1,2]. Long term use of these drugs causes various side effects such as ulceration, gastrointestinal bleeding and heart stroke [3,4] All these indicate that there is a need for safer anti-inflammatory drugs.

Amidine derivatives exhibiting anti-inflammatory [5], anti-degenerative [6], antiplatelet [7], anticancer [8,9], antimicrobial [10], urokinase inhibitor [11] and amide derivatives possessing anti-inflammatory [12–15] antimicrobial [16] antitubercular [17] activities have been reported in the literature. Tempted by wide variety of biological activities shown by amidine and amide derivatives and in continuation [18–22] of our efforts in search of potent, molecules exhibiting anti-inflammatory and analgesic activities we report herewith synthesis, anti-inflammatory and analgesic activity evaluation of various amidine and amide derivatives.

2. Results and discussion

2.1. Chemistry

Various 3,4-diaryl-2-imino-4-thiazolines (**1a**–**i**, Scheme 1) were synthesized by condensation of amine hydrochlorides with phenacylthiocyanates as reported in the literature [23]. 2-Cyanopyridine on refluxing with 3-(4-methoxyphenyl)-4-phenyl-2-imino-4-thiazoline (**1a**; Scheme 1) in methanol for 8 h gave condensed product **2a** (Scheme 1) after usual workup. Compound **2a** was purified by crystallization from methanol to give pure *N*-[3-(4-methoxyphenyl)-4-phenyl thiazol-2-(3*H*)-ylidene] picolinamidine (**2a**, Scheme 1) in 91% yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **2a** shows signals at δ 3.77 (s, 3H, OCH_3), 6.97–6.99 (d, 3H, Ar), 7.22–7.23 (t, 4H, Ar), 7.27–7.29 (t,3H, Ar), 7.40–7.43 (m, 1H, py), 7.73–7.74 (d, 1H, py), 7.82–7.85 (m,1H, py), 8.64–8.65 (d,1H, py), 10.11 (br s, 1H, NH, exch). FAB-MS *m*/*z* 387 (MH^+ 100%). FT-IR spectra show absorption band at 3239 (NH), 1632 (C═N), 1543 and 1513 (Ar) cm^{-1} Spectral data of **2a** fully support the structure assigned to it. Similarly other amidine derivatives i.e. **2b**–**i** (Scheme 1) were synthesized and purified by crystallization. Spectral and analytical data of compounds **2a**–**i** reported in Section 4 of this paper fully support the structures assigned to them.

Various amide derivatives (**3a**–**h**; Scheme 1) were synthesized by using microwave irradiation under solvent free reaction condition. Thus equimolar ratio of 3-(4-methoxyphenyl)-4-phenyl-2-imino-4-thiazoline (**1a**, Scheme 1) and orotic acid were taken

* Corresponding author. Tel.: +91 1332 285811; fax: +91 1332 273650.
E-mail address: sondifcy@iitr.ernet.in (S.M. Sondhi).

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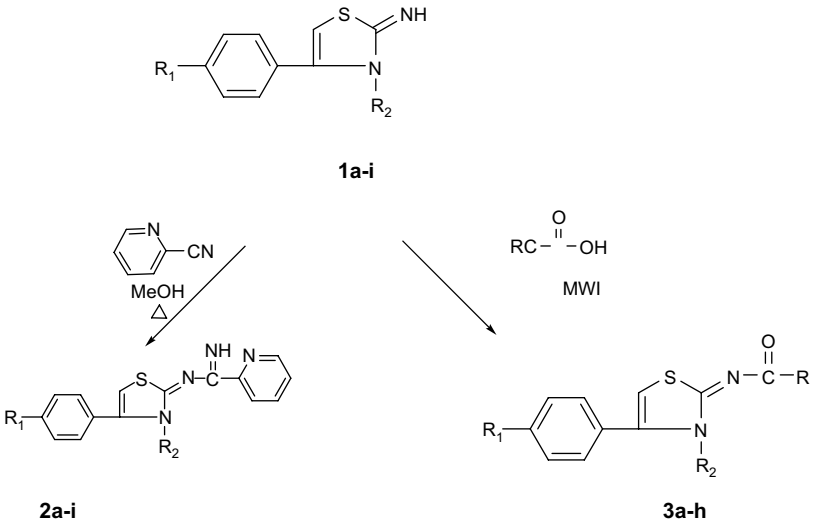


	R_1	R_2		R_1	R_2	R
2a	H	4-OMe	**3a**	H	4-OMe	
2b	H	4-$COCH_3$	**3b**	H	4-$COCH_3$	
2c	H	4-Cl	**3c**	H	4-Cl	
2d	H	4-NO_2	**3d**	OCH_3	4-NO_2	
2e	H	2-NO_2	**3e**	H	2-NO_2	
2f	OC_2H_5		**3f**	H	4-Cl	
2g	H	3-Me	**3g**	H	4-NO_2	
2h	H	3-MeO	**3h**	H	2-NO_2	
2i	Br					

Scheme 1.

together in a petri dish. Both the reactants were mixed thoroughly and then subjected to microwave irradiation for 20 min at a power level of 450 W. The reaction contents were taken in hot methanol and filtered to remove any insoluble material. From the filtrate so obtained solvent was removed under reduced pressure to give the crude product. This crude product was washed thoroughly with ethyl acetate and the solid product left behind was purified by crystallization from methanol to give *N*-[3-(4-methoxyphenyl)-4-phenyl thiazol-2(3*H*) ylidene]-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (**3a**, Scheme 1) in 80% yield. ^{1}H NMR (500 MHz, DMSO-d_6) of **3a** shows signals at δ 3.75 (s, 3H, OCH_3), 5.74 (s, 1H, >C═CH–), 7.02–7.03 (d, 2H, Ar), 7.13 (s,1H, Ar), 7.18–7.20 (d, 2H, Ar), 7.21–7.34 (m, 3H, Ar), 7.39–7.41 (d, 2H, Ar), 9.27 (s, 1H, NH, exch), 10.95 (s, 1H, NH, exch). GC–MS *m*/*z* 420 (M^+, 43.26%). FT-IR spectra show absorption bands at 3450 (NH), 1703 (>C═O), 1631 (>C═N–), 1532 and 1508 (Ar) cm^{-1}. Spectral data of **3a** fully support the structure assigned to it. Following similar procedure of other amide derivatives i.e. **3b**–**h** (Scheme 1) were synthesized and purified by crystallization. Spectral and analytical data of **3a**–**h** reported in Section 4 of this paper is in agreement with the structures assigned to them. ^{1}H NMR of compounds reported in this paper was taken after six months from synthesizing them and no change was observed in the ^{1}H NMR, similarly ^{1}H NMR (DMSO-d_6) of compounds solution in DMSO-d_6 taken after keeping them for ten days at room temperature did not show any change. From these observations it is clear that the compounds reported in this paper are very stable in solid as well in liquid phase.

2.2. Biological results

Anti-inflammatory activity [24] evaluation of **2a**–**i** and **3a**–**h** was carried out using carrageenan induced paw oedema assay and

results are summarized in Table 1. Compounds **2a–i** and **3a–h**, at 50 mg/kg p.o. exhibited 17%, 20%, 17%, 26%, 49%, 0.0%, 0.0%, 23%, 0.0% and 9%, 12%, 2%, 15%, 25%, 10% 34% and 17% activity, respectively whereas ibuprofen exhibited 39% anti-inflammatory activity at 50 mg/kg p.o. Analgesic activity [25] evaluation was carried out using acetic acid writhing assay and results are summarized in Table 1. Compounds **2a–d**, **f**, **g**, **i** and **3a**, **b**, **d**, **f** at 50 mg/kg p.o. exhibited 12%, 25% 12%, 18%, 50%, 50% 40% and 8%, 8%, 10% 0.0% analgesic activity, respectively, whereas ibuprofen exhibited 50% analgesic activity at 50 mg/kg p.o. A look at the Table 1 indicates that compounds **2e** and **3g** exhibited good anti-inflammatory whereas compounds **2f** and **g** exhibited good analgesic activity.

2.2.1. Structure–activity relationship

Aryl group substituted at position 3 of compound **2** is substituted at its *ortho* or *para* position. Anti-inflammatory activity is increased when aryl group is substituted at its *ortho* position by $-NO_2$ group (**2e**), whereas substitution by –Me group (**2g**) at *ortho* position or no substitution on phenyl ring (**2f**) is favorable for analgesic activity. In case of compound **3** substitution by $-NO_2$ group at *para* position of phenyl ring (**3g**) is beneficial for anti-inflammatory activity. Lipophilicity ($C\log P$) values for the compounds **2a–i** and **3a–h** were estimated by using ChemDraw Ultra and were found to be 6.228, 5.748, 7.022, 6.052, 6.052, 6.309, 6.808, 6.228, 7.483 and 4.098, 3.618, 4.892, 3.841, 3.922, 4.75, 3.78, 3.78, respectively. From lipophilicity point of view compounds **2e** and **f** have lipophilicity values 6.052 and 6.309 but they show 49% and 0.0% anti-inflammatory activity. Similarly compounds **3g** and **h** have lipophilicity values 3.78 and 3.78 but they show 34% and 17% anti-inflammatory activity. Compounds **2c** and **g** have lipophilicity values 7.022 and 6.808 but they show analgesic activity 12% and 50%, respectively. From the above discussion it can be concluded that molecules which meet lipophilicity, stereochemical and electronic requirements of the target in a better way exhibited good anti-inflammatory and analgesic activities.

3. Conclusion

A number of amidine (**2a–i**) and amide (**3a–h**) derivatives have been synthesized and characterized by spectroscopic means. On anti-inflammatory and analgesic activity screening of **2a–i**, **3a–h** and **2a–d**, **f**, **g**, **i**; **3a**, **b**, **d**, **f**, respectively, compounds **2e**, **3g** exhibited good anti-inflammatory activity and compounds **2f** and **g** exhibited good analgesic activity.

Table 1
Anti-inflammatory and analgesic activity evaluation of compounds **2a–i** and **3a–h**

Compounds tested	Anti-inflammatory activity		Analgesic activity	
	Dose mg/kg p.o.	Activity %	Dose mg/kg p.o.	Activity %
2a	50	17	50	12
2b	50	20	50	25
2c	50	17	50	12
2d	50	26	50	18
2e	50	49	50	NT
2f	50	0.0	50	50
2g	50	0.0	50	50
2h	50	23	50	NT
2i	50	0.0	50	40
3a	50	9.0	50	8.0
3b	50	12	50	8.0
3c	50	2.0	50	NT
3d	50	15	50	10
3e	50	25	50	NT
3f	50	10	50	0.0
3g	50	34	50	NT
3h	50	17	50	NT
Aspirin	50	43	–	–
Ibuprofen	50	39	50	50

4. Experimental

4.1. General

Melting points (mp) were determined on a JSGW apparatus and are uncorrected. Domestic microwave oven model M 197 DL (SAMSUNG) was used for microwave irradiation. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer ^{1}H NMR spectra were recorded on a Bruker WH-500 and 300 spectrometer at a ca 5–15% (w/v) solution in DMSO-d_6 (TMS as internal standard) FAB-MS was recorded on JEOL SX-120 (FAB) spectrometer. GC–MS was recorded on Perkin Elmer Clarus 500 mass spectrometer. 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). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

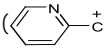
4.2. General procedure for the synthesis of amidine derivatives (*2a–i*)

4.2.1. N-*(3-(4-Methoxyphenyl)-4-phenylthiazol-2(*3H*)-ylidene)picolinamidine (**2a**)*

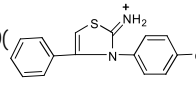
3-(4-Methoxyphenyl)-4-phenyl thiazol-2(3*H*)-imine 0.282 g (1 mmol) was taken in 15 ml methanol and to it was added 0.104 g (1 mmol) 2-cyanopyridine. Reaction contents were heated under reflux for 8 h. Solvent was removed under reduced pressure and the residue left behind was scratched with diethyl ether, solid separated out was filtered and air dried to give crude product, which was purified by crystallization from methanol to give pure product **2a**. Yield: 0.352 g (91%); mp: 210 °C; IR (KBr) ν_{max}: 3239 (NH), 1632 (>C═N–), 1543 and 1513 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 6.97–6.99 (d, $J = 9.5$ Hz, 3H, Ar), 7.22–7.23 (t, 4H, Ar), 7.27–7.29 (t, 3H, Ar), 7.40–7.43 (m, 1H, Py), 7.73–7.74 (d, $J = 7.5$ Hz 1H, Py), 7.82–7.85 (m, 1H, Py), 8.64–8.65 (d, $J = 4$ Hz, 1H, Py), 10.11 (s, 1H, NH, exch) FAB-MS m/z 387 (MH^+, 100%). Anal. Calcd for $C_{22}H_{18}N_4OS$ C, 68.39; H, 4.68; N, 14.50; S, 8.29. Found C, 68.51; H, 4.34; N, 14,15; S, 8.31.

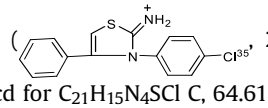
Similarly were synthesized compounds **2b–i**.

4.2.2. N-*(3-(4-Acetylphenyl)-4-phenyl thiazol-2(*3H*)-ylidene)picolinamidine (**2b**)*

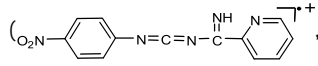
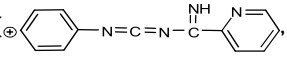
Solvent of crystallization: MeOH; Yield: 69%; mp: 245 °C; IR (KBr) ν_{max}: 3236 (NH), 1679 (C═O), 1598 (>C═N–), 1571 and 1517(Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.61 (s, 3H, CH_3), 7.07 (s, 1H, >C═CH–), 7.23–7.29 (m, 5H, Ar), 7.42–7.44 (q, 1H, Ar), 7.55–7.57 (d, $J = 8$ Hz, 2H, Ar), 7.70–7.72 (d, $J = 7.5$ Hz, 1H, Py), 7.82–7.85 (t, $J = 7.5$ Hz, 1H, Py), 8.02–8.04 (d, $J = 8.5$ Hz, 2H, 1H(Ar)+1H(Py)), 8.65–8.66 (d, $J = 4.5$ Hz, 1H, Py), 10.21 (s, 1H, NH, exch). FAB-MS m/z 399 (MH^+, 15.52%), 398 (M^+, 100%), 105 ( , 11.4%). Anal. Calcd for $C_{23}H_{18}N_4OS$ C, 69.34; H, 4.52; N, 14.07; S, 8.04. Found C, 69.58; H, 4.60, N, 14.45; S, 8.35.

4.2.3. N-*(3-(4-Chlorophenyl)-4-phenyl thiazol-2(*3H*)-ylidene)picolinamidine (**2c**)*

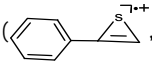
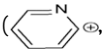
Solvent of crystallization: MeOH; Yield: 91%; mp: 215 °C; IR (KBr) ν_{max}: 3256 (NH), 1639 (>C═N–), 1545, 1508 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.06 (s, 1H, >C═CH–), 7.22–7.24 (m, 2H, Ar), 7.30–7.32 (t, $J = 5$ Hz, 3H, Ar), 7.43–7.45 (m, 3H, Ar), 7.52–7.53 (d, $J = 5$ Hz, 2H, Ar), 7.72–7.74 (d, $J = 10$ Hz, 1H, Py), 7.86–7.89 (m, 1H, Py), 8.66 (d, 1H, Py), 10.17 (s, 1H, NH, exch). APCI-MS m/z 393 ($MH^+ + 2$, 33.33%), 391 (MH^+, 100%), 289( , 6%),

287 ( , 20%), 105 (5%). Anal. Calcd for $C_{21}H_{15}N_4SCl$ C, 64.61; H, 3.84; N, 14.36; S, 8.20. Found C, 64.73; H, 3.57; N, 14.37; S, 8.00.

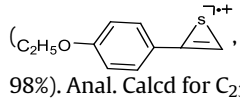
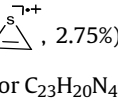
4.2.4. N-*(3-(4-Nitrophenyl)-4-phenyl thiazol-2(3*H*)-ylidene)picolinamidine (**2d**)*

Solvent of crystallization: MeOH; Yield: 70%; mp: 215 °C; IR (KBr) ν_{max}: 3230 (NH), 1636 (>C═N–), 1595 and 1515 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.10 (s, 1H, >C═CH–), 7.24–7.25 (d, $J = 5$ Hz, 2H, Ar), 7.30-7.31 (d, $J = 4$ Hz, 3H, Ar), 7.42–7.44 (t, 1H, Ar), 7.71-7.73 (d, $J = 9$ Hz, 3H, Ar), 7.83–7.86 (t, 1H, Py), 8.30–8.32 (d, $J = 8.5$ Hz, 2H, Py), 8.65–8.66 (d, $J = 4$ Hz, 1H, Py), 10.27 (s, 1H, NH, exch). GC–MS *m*/*z* 401 (M^+, 0.81%), 355 (M^+-NO_2, 7.59%), 267 ( , 2.19%), 221 ( , 19.94%). Anal. Calcd for $C_{21}H_{15}N_5O_2S$ C, 62.84; H, 3.74; N, 17.45; S, 7.98. Found C, 62.76; H, 3.67; N, 17.67; S, 8.03.

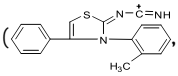
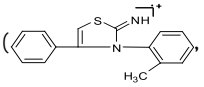
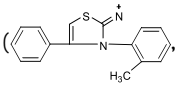
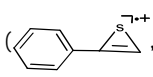
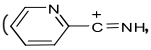
4.2.5. N-*(3-(2-Nitrophenyl)-4-phenyl thiazol-2(3*H*)-ylidene)picolinamidine (**2e**)*

Solvent of crystallization: MeOH; Yield: 62%; mp: 190 °C; IR (KBr) ν_{max}: 3252 (NH), 1611 (>C═N–), 1531 and 1506 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.13 (s, 1H, >C═CH–), 7.32 (s, 5H, Ar), 7.36–7.38 (t, 1H, Ar), 7.42–7.44 (t, 1H, Ar), 7.57–7.58 (d, $J = 8$ Hz, 1H, Ar), 7.72–7.73 (t, 2H, 1H(Ar)+1H(Py)), 7.83–7.84 (t, $J = 7.5$ Hz, 1H, Py), 8.25–8.27 (t, 1H, Py), 8.64–8.65 (d, $J = 4$ Hz, 1H, Py), 10.22 (s, 1H, NH, exch). GC–MS *m*/*z* 401 (M^+, 30.95%), 134 ( , 51.41%), 78 ( , 100%). Anal. Calcd for $C_{21}H_{15}N_5O_2S$ C, 62.84; H, 3.74; N, 17.45; S, 7.98. Found C, 62.76; H, 3.67; N, 17.67; S, 8.03.

4.2.6. N-*(4-(4-Ethoxyphenyl)-3-phenyl thiazol-2(3*H*)-ylidene)picolinamidine (**2f**)*

Solvent of crystallization: MeOH; Yield: 71%; mp: 182 °C; IR (KBr) ν_{max}: 3251 (NH), 1615 (>C═N–), 1546 and 1494 (Ar) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.35–1.39 (t, 3H, CH_3), 3.95–4.02 (q, 2H, CH_2), 6.65 (s, 1H, >C═CH–), 6.71-6.74 (d, $J = 8.7$ Hz, 2H, Ar), 7.05–7.08 (d, $J = 8.6$ Hz, 2H, Ar) 7.28–7.35 (m, 3H, Ar), 7.38–7.42 (m, 3H, 2H(Ar)+1H(Py)), 7.68–7.71(m, 1H, Py), 7.78–7.81 (d, $J = 7.6$ Hz, 1H, Py). 8.60–8.61 (d, $J = 4.5$ Hz, 1H, Py), 10.10 (s, 1H, NH, exch). GC–MS *m*/*z* 400 (M^+, 15.83%), 279 (M^+-*m*/*z* 121, 8%) 178 ( , 2.75%), 121 ( , 18%), 77 ($C_6H_5^+$, 98%). Anal. Calcd for $C_{23}H_{20}N_4OS$ C, 69.00; H, 5.00; N, 14.00; S, 8.00. Found C, 68.72; H, 4.9; N, 13.78; S, 7.7.

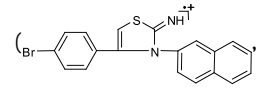
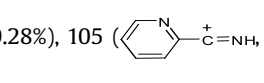
4.2.7. N-*(4-Phenyl-3-*o*-tolyl thiazol-2(3*H*)-ylidene)picolinamidine (**2g**)*

Solvent of crystallization: MeOH; Yield: 79%; mp: 164 °C; IR (KBr) ν_{max}: 3253 (NH), 1633 (>C═N–), 1541 and 1494 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.05 (s, 3H, CH_3) 7.04 (s, 1H, >C═CH–), 7.202–7.215 (d, $J = 6.5$ Hz, 2H, Ar), 7.24–7.27 (m, 5H, Ar), 7.341–7.355 (d, $J = 7$ Hz, 2H, Ar), 7.38–7.40 (m, 1H, Py), 7.545–7.560 (d, $J = 7$ Hz, 1H, Py), 7.752–7.769 (m, 1H, Py), 8.627–8.635 (d, $J = 4$ Hz, 1H, Py), 10.08 (s, 1H, NH, exch). GC–MS *m*/*z* 370 (M^+, 5.49%), 355 (M^+–•CH_3; 1.43%), 292 ( , 4.87%), 266 ( , 4.89%), 265 ( , 4.41%), 134 ( , 21.04%), 105 ( , 23.36%). Anal. Calcd for $C_{22}H_{18}N_4S$ C, 71.35; H, 4.86; N, 15.13; S, 8.65. Found C, 71.02, H, 4.3; N, 14.95; S, 8.25.

4.2.8. N-*(3-(2-Methoxyphenyl)-4-phenyl thiazol-2(3*H*)-ylidene)picolinamidine (**2h**)*

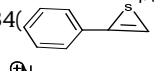
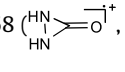
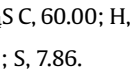
Solvent of crystallization: MeOH; Yield: 55%; mp: 235 °C; IR (KBr) ν_{max}: 3257 (NH), 1599 (>C═N–), 1549 and 1493 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.57 (s, 3H, OCH_3), 6.96 (s, 1H, >C═CH–), 7.06–7.11 (m, 2H, Ar), 7.21–7.22 (m, 2H, Ar), 7.25–7.28 (m, 3H, Ar), 7.40–7.44 (m, 3H, 2H(Ar)+1H(Py)), 7.63–7.64 (d, $J = 8$ Hz, 1H, Py), 7.78–7.81 (m, 1H, Py), 8.64–8.65 (d, $J = 4.5$ Hz, 1H, Py), 10.08 (s, 1H, NH, exch). FAB-MS *m*/*z* 387 (MH^+, 100%). Anal. Calcd for $C_{22}H_{18}N_4OS$ C, 68.39; H, 4.68; N, 14.50; S, 8.29. Found C, 68.76; H, 5.02; N, 14.55, S, 8.28.

4.2.9. N-*(4-(4-Bromophenyl)-3-(naphthalen-2-yl)thiazol-2(3*H*)-ylidene)picolinamidine (**2i**)*

Solvent of crystallization: MeOH; Yield: 94%; mp: 180 °C; IR (KBr) ν_{max}: 3439 (NH), 1630 (>C═N–), 1577 and 1550 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 7.07 (s, 1H, >C═CH–), 7.121–7.138 (d, $J = 8.5$ Hz, 2H, Ar), 7.29–7.31 (m, 1H, Ar), 7.35–7.37 (d, $J = 8.5$ Hz, 2H, Ar), 7.46–7.58 (m, 4H, Ar), 7.63–7.66 (t, $J = 7.5$, 1H, Ar), 7.81–7.85 (m, 2H, 1H(Ar)+1H(Py)), 7.93–7.94 (d, $J = 8$ Hz, 1H, Py), 7.97–7.99 (d, $J = 8.5$ Hz, 1H, Py), 8.55–8.56 (d, $J = 4.5$ Hz, 1H, Py), 10.12 (s, 1H, NH, exch). MS *m*/*z* 486 (M + 1, 100%), 381 ( , 35.77%), 380 ( , 39.28%), 105 (, 3.57%). Anal. Calcd for $C_{25}H_{17}N_4SBr$ C, 61.85; H, 3.50; N, 11.54; S, 6.59. Found C, 61.55; H, 3.20; N, 11.85; S, 6.29.

*4.3. General procedure for the synthesis of amide derivatives (**3a**–**h**)*

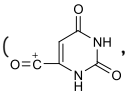
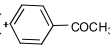
4.3.1. N-*(3-(4-Methoxyphenyl)-4-phenyl thiazol-2(3*H*)-ylidene)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (**3a**)*

3-(4-Methoxyphenyl)-4-phenyl-2-imino-4-thiazoline (0.282 g, 1 mmol) and orotic acid (0.156 g, 1 mmol) were taken together in a petri dish. Both the reactants were mixed thoroughly and then subjected to microwave irradiation for 20 min at a power level of 450 W. The reaction contents were taken in hot methanol and filtered to remove any insoluble materials. From the filtrate so obtained solvent was removed under reduced pressure to give the crude product. This crude product was washed thoroughly with ethyl acetate and the solid product left behind was purified by crystallization from methanol to give **3a**. Yield: 0.340 g (80%); mp: 225 °C; IR (KBr) ν_{max}: 3450 (NH), 1703 (>C═O), 1631 (>C═N–), 1532, 1550 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.57 (s, 3H, OCH_3), 5.74 (s, 1H, ═CH–), 7.02–7.03 (d, $J = 9$ Hz, 2H, Ar), 7.13 (s, 1H, Ar), 7.18–7.20 (d, $J = 7$ Hz, 2H, Ar), 7.21–7.34 (m, 3H, Ar), 7.39–7.41 (d, $J = 9$ Hz, 2H, Ar), 9.27 (s, 1H, NH, exch), 10.95 (s, 1H, NH, exch). GC–MS *m*/*z* 420 (M^+, 43.26%), 389 (M^+ OCH_3, 12.47%), 343 (M^+–•C_6H_5; 23.46%), 134( ,9.07%), 111( , 89.55%), 58 ( , 17.13%), 57 ( , 100%). Anal. Calcd for $C_{21}H_{16}N_4O_4S$ C, 60.00; H, 3.81; N, 13.33; S, 7.61. Found C, 59.65; H, 4.20; N, 13.15; S, 7.86.

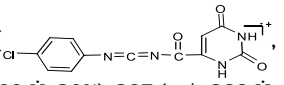
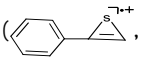
Similarly were synthesized compounds **3b**–**h**.

4.3.2. N-*(3-(4-Acetylphenyl)-4-phenyl thiazol-2(3*H*)-ylidene)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (**3b**)*

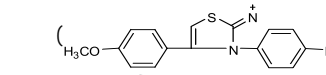
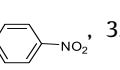
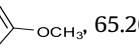
Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 51%; mp: 145 °C; IR (KBr) ν_{max}: 3430 (NH),

1686 (>C=O), 1613 (>C=N–), 1530, 1488 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.42 (s, 3H, $COCH_3$), 5.69(s, 1H, =CH–), 7.07 (s, 1H, >C=CH–), 7.11–7.13 (m, 2H, Ar), 7.20–7.25 (m, 3H, Ar), 7.55–7.57 (d, $J = 8$ Hz, 2H, Ar), 7.95–7.97 (d, $J = 9$ Hz, 2H, Ar), 9.58 (s, 1H, NH, exch), 10.97 (s, 1H, NH, exch). GC–MS m/z 432 (M^+, 29.96%), 139 ( , 16.4%), 119 ( , 7.82%). Anal. Calcd for $C_{22}H_{16}N_4O_4S$ C, 61.11; H, 3.70; N, 12.96; S, 7.40. Found C, 60.83; H, 3.35; N, 13.20; S, 7.24.

4.3.3. N-(3-(4-Chlorophenyl)-4-phenyl thiazol-2(3H)-ylidene)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (**3c**)

Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 84%; mp: 155 °C; IR (KBr) ν_{max}: 3447 (NH), 1733 (>C=O), 1618(>C=N–), 1533 and 1486 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 5.73 (s, 1H, =CH–), 7.11 (s, 1H, >C=CH–), 7.18–7.20 (d, $J = 7$ Hz, 2H, Ar), 7.29–7.35 (m, 3H, Ar), 7.52–7.54 (d, $J = 8.5$ Hz, 2H, Ar), 7.57–7.59 (d, $J = 8.5$ Hz, 2H, Ar), 9.52 (s,1H, NH, exch), 10.93 (s. 1H, NH, exch). FAB-MS does not give M^+ ion peak but gave m/z 313 (M^+-m/z 111, 2.77%), 290 ( , 25%), 289 (m/z 290 H, 90%), 288 (m/z 289 Ḣ, 20%), 287 (m/z 288 Ḣ, 100%), 134 ( , 4.14%), 111 ( , 2.77%). Anal. Calcd for $C_{20}H_{13}N_4O_3SCl$ C, 56.60; H, 3.06; N, 13.20; S, 7.54. Found C, 57.03; H, 3.47; N, 13.65; S, 7.23.

4.3.4. N-(4-(4-Methoxyphenyl)-3-(4-nitrophenyl)thiazol-2(3H)-ylidene)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide (**3d**)

Solvent of crystallization: MeOH; Power level: 300 W, Irradiation time: 25 min; Yield: 60%; mp: 215 °C; IR (KBr) ν_{max}: 3400 (NH), 1683 (>C=O), 1606(>C=N–), 1528, 1493 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.72 (s, 3H, OCH_3), 5.76 (s, 1H, =CH–), 6.86–6.87 (d, $J = 8$ Hz, 2H, Ar), 6.99 (s, 1H, >C=CH–), 7.13–7.15 (d, $J = 7.5$ Hz, 2H, Ar), 7.78–7.80 (d, $J = 7.5$ Hz, 2H, Ar), 8.36–8.38 (d, $J = 8.5$ Hz, 2H, Ar), 9.69 (s, 1H, NH, exch), 11.00 (s, 1H, NH, exch). GC–MS m/z 465 (M^+, 4.25%),358 (M^+-m/z 107, 3.06%). 326 ( , 3.06%), 122 ( , 79.87%), 107 ( , 65.26%), Anal. Calcd for $C_{21}H_{15}N_5O_6S$ C, 54.19; H, 3.22; N, 15.05; S, 6.88. Found C, 54.43; H, 2.95; N, 15.45; S, 6.65.

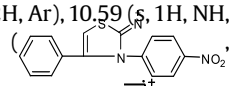
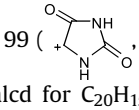
4.3.5. N-(3-(2-Nitrophenyl)-4-phenyl thiazol-2(3H)-ylidene)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide(**3e**)

Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 68%; mp: 220 °C; IR (KBr) ν_{max}: 3250 (NH), 1688 (>C=O), 1533, 1486 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 5.78 (s, 1H,), 6.99 (s, 1H, >C=CH–), 7.12–7.13 (t, 2H, Ar), 7.25–7.33 (m, 3H, Ar), 7.72–7.77 (m, 2H, Ar), 7.84–7.88 (m, 1H, Ar), 8.16–8.17 (dd, 1H, Ar), 9.84 (s, 1H, NH, exch), 11.02 (s, 1H, NH, exch). FAB-MS does not give M^+ ion peak but gave 392 (M^+-HNCO, 2%). Anal. Calcd for $C_{20}H_{13}N_5O_5S$ C, 55.17; H, 2.98; N, 16.09; S, 7.35. Found C, 55.42; H; 3.02; N, 15.95; S, 7.80.

4.3.6. N-(3-(4-Chlorophenyl)-4-phenylthiazol-2(3H)-ylidene)-2-(2,5-dioxoimidazolidin-4-yl)acetamide (**3f**)

Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 67%; mp: 200 °C; IR (KBr) ν_{max}: 3441 (NH), 1721 (>C=O), 1615(>C=N–), 1532 and 1487 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.577–2.598 (t, 2H, CH_2), 4.16–4.19 (t, 1H, imidazolidin), 6.34 (s, 1H, >C=CH–), 7.10–7.12 (m, 2H, Ar), 7.17–7.19 (d, $J = 8.5$ Hz, 2H, Ar), 7.23–7.24 (m, 3H, Ar), 7.37–7.39 (d, $J = 9$ Hz, 2H, Ar), 7.80 (s, 1H, NH, exch), 10.59 (s, 1H, NH, exch). FAB-MS does not give M^+ ion peak but gave 391 (M^+−Cl, 1%). Anal. Calcd for $C_{20}H_{15}N_4O_3SCl$ C, 56.33; H, 3.52; N, 13.14; S, 7.51. Found C, 56.02; H, 3.92; N, 13.53; S, 7.83.

4.3.7. 2-(2,5-Dioxoimidazolidin-4-yl)-N-(3-(4-nitrophenyl)-4-phenyl thiazol-2(3H)-ylidene)acetamide (**3g**)

Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 84%; mp: 215 °C; IR (KBr) ν_{max}: 3194 (NH), 2916 (CH_2), 1765, 1712 (>C=O), 1534, 1495 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 2.60–2.61 (d, $J = 5$ Hz, 2H, CH_2), 4.18–4.20 (t, $J = 5$; 10.5 Hz, 1H, imidazolidin), 6.42 (s, 1H, >C=CH–), 7.11–7.13 (m, 2H, Ar), 7.24–7.25 (m, 3H, Ar), 7.41–7.43 (d, $J = 9$ Hz, 2H, Ar), 7.85 (s.1H, NH, exch), 8.14–8.16 (d, $J = 9$ Hz, 2H, Ar), 10.59 (s, 1H, NH, exch), GC–MS m/z 437 (M,$^+$ 1.32%), 296 ( , 31.34%), 99 ( , 2.87%), 77 ($C_6H_5^+$, 21.07%), 76 ($C_6H_4^+$, 100%). Anal. Calcd for $C_{20}H_{15}N_5O_5S$ C, 54.91; H, 3.43; N, 16.01; S, 7.32. Found C, 55.23; H, 3.02; N, 15.85; S, 7.73.

4.3.8. 2-(2,5-Dioxoimidazolidin-4-yl)-N-(3-(2-nitrophenyl)-4-phenylthiazol-2(3H)-ylidene)acetamide (**3h**)

Solvent of crystallization: MeOH; Power level: 450 W, Irradiation time: 20 min; Yield: 74%; mp: 175 °C; IR (KBr) ν_{max}: 3320 (NH), 1700 (>C=O), 1581, 1531 (Ar) cm.$^{-1}$ ^1H NMR (500 MHz, DMSO-d_6) δ: 2.60–2.61 (d, $J = 5.5$ Hz, 2H, CH_2), 4.18–4.20 (t, $J = 5$; 10 Hz, 1H, imidazolidin), 6.37 (s, 1H, >C=CH–), 7.14–7.22 (m, 3H, Ar), 7.23–7.25 (m, 3H, Ar), 7.50–7.53 (m, 1H, Ar), 7.57–7.61 (m, 1H, Ar), 7.82 (s, 1H, NH, exch), 8.01–8.03 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, 1H, Ar), 10.59 (s, 1H, NH, exch). FAB-MS does not give M^+ ion peak but gave 391 (M^+−NO_2, 2.77%). Anal. Calcd for $C_{20}H_{15}N_5O_5S$ C, 54.91; H, 3.43; N, 16.01; S, 7.32. Found C, 54.59; H, 3.72; N, 16.43; S, 7.02.

4.4. Anti-inflammatory activity

Paw oedema inhibition test was used on albino rats of charles Foster by adopting the method of Winter et al. [24] Groups of five animals of both sexes (body weight 120–160 g), excluding pregnant females, were given a dose of test compound. Thirty minutes 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 is 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 **2a–i** and **3a–h** were screened for anti-inflammatory activity and results are summarized in Table 1.

4.5. Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis et al. [25] groups of five mice of both sexes (body weight 20–30 g), pregnant females excluded, were given a dose of test compound. Thirty minutes later, the animals were injected 0.25 ml/mice of 0.5% acetic acid solution and writhes were counted during the following 60 min. The mean number of writhes of each

experimental group and percent decrease compared with control group (five mice not treated with test compounds) were calculated.

Compounds **2a**–**d**, **f**, **g**, **i** and **3a**, **b**, **d**, **f** were screened for analgesic activity and results are summarized in Table 1.

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