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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of biological and nonlinear optical properties of some novel 2,4-disubstituted [1,3]-thiazoles carrying 2-(aryloxymethyl)-phenyl moiety

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Abstract A series of 2,4-disubstituted-[1,3]-thiazoles (**4a–p** and **6a–l**) was synthesized from 2-(aryloxymethyl)benzoic acids (**1a–d**) through a multistep reaction sequence in good yield. The structures of the new compounds were established on the basis of their elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. All the synthesized compounds were screened for their antimicrobial and anti-inflammatory activities. Preliminary results indicated that some of them exhibit promising activities and they deserve more consideration as potential antimicrobial and anti-inflammatory agents. The nonlinear optical (NLO) property of **4a–p** was also studied. The compound **4n** with 2-(3-methylphenoxymethyl)phenyl and 4-nitrophenyl substituents showed very good NLO property compared to other compounds and also the reference compound, urea.

Keywords 2-(Aryloxymethyl)benzothioamides · 2,4-Disubstituted thiazoles · Antimicrobial activity · Anti-inflammatory activity

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Introduction

Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycin and Tiazofurin (antineoplastic drug). Different thiazole-bearing compounds possess antimicrobial, analgesic and anti-inflammatory properties (Prakash *et al*., 2008; Wagle *et al*., 2008; Venugopala and Jayashree, 2003; Holla *et al*., 2003; Karabasanagouda *et al*., 2008). They have been also used as chemosensors, sedatives, hypnotics as well as agrochemical products (El-Subbagh and Al-Obaid, 1996; Aasif and Hong-Seok, 2009; Beck *et al*., 1998; Gregory *et al*., 2001; Kempf *et al*., 1998; Quiroga *et al*., 2002; Hutchinson *et al*., 2002). Recently, the applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity and as new inhibitors of bacterial DNA gyrase B (Hargrave *et al*., 1983; Patt *et al*., 1992; Sharma *et al*., 2009; Jaen *et al*., 1990; Tsuji and Ishikawa, 1994; Bell *et al*., 1995; Ergenc *et al*., 1999, Carter *et al*., 1999; Badorc *et al*., 1997; Rudolph *et al*., 2001; Holla *et al*., 2002). Prompted by these investigations and in continuation of our search for bioactive molecules, we have herein reported the synthesis of some 2,4-disubstituted-[1,3]-thiazoles (Fig. 1) starting from 2-(aryloxymethyl)benzothioamides, 1,3-dichloroacetone, various substituted phenacyl bromides and secondary amines/substituted phenols (Scheme 1) and tested them for their anti-inflammatory, antibacterial and antifungal properties.

The nonlinear optical (NLO) properties of the organic molecular crystals have received a great deal of interest for

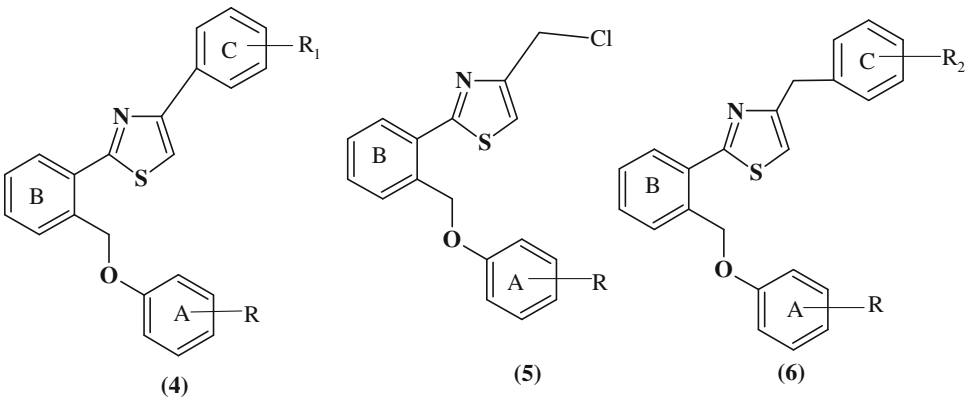
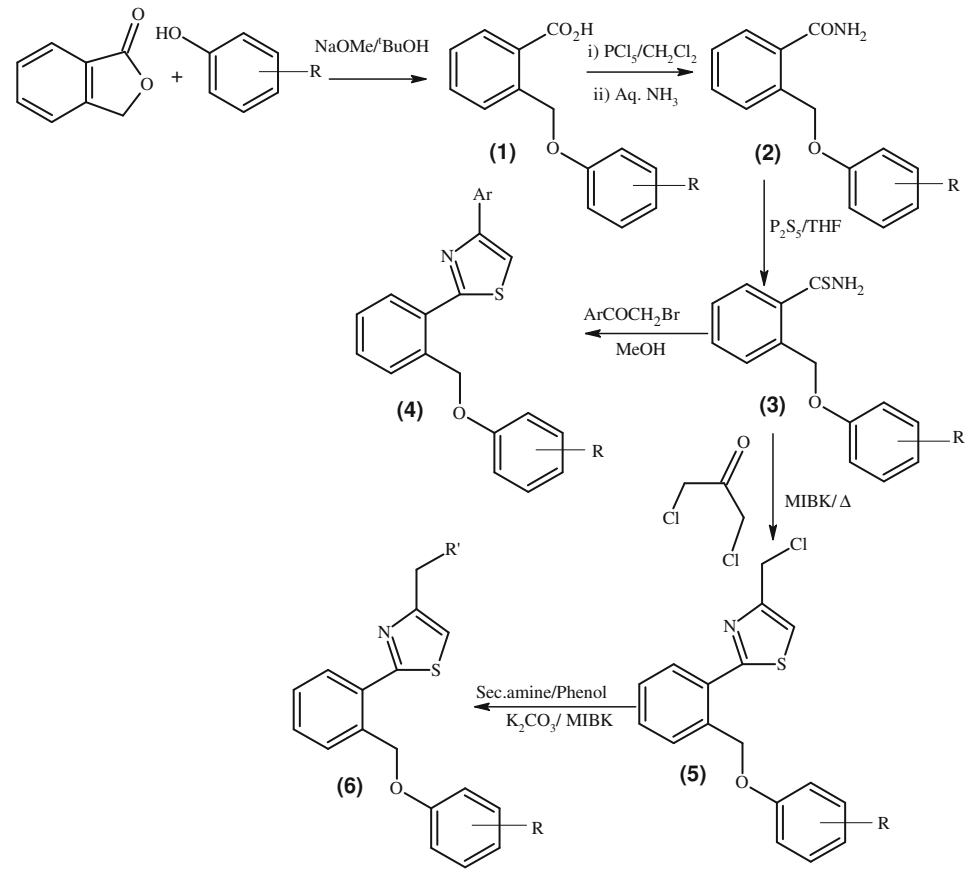


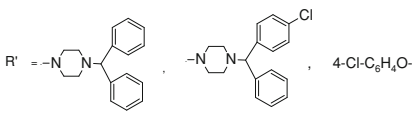
Fig. 1 General structures of 2-[2-(aryloxymethyl)phenyl]-4-substituted-[1,3]-thiazoles (**4a–p**) and (**6a–l**)



Scheme 1 Synthetic route for 4-aryl-[2-(aryloxymethyl) phenyl]-[1,3]-thiazoles (**4a–p**) and (**6a–l**)

R= 2-CH_3, 3-CH_3 , 4-CH_3, 4-Cl.

Ar = 3-$CONH_2$-4-OH- C_6H_3, 5-Cl-2- SO_2NH_2-3-thienyl, 3-Br-C_6H_4, 4-NO_2-C_6H_4



the past two decades due to their extensive application in the fields like laser technology, telecommunication, optical information processing and storage (Chemla and Zyss, 1987; Wang *et al*., 1999). It is known that thiazoles and its derivatives showed some interesting physical properties other than biological properties (Mashraqui *et al*., 2006; Man He *et al*., 2010). Prompted by such observations, it was contemplated to study the NLO properties of a series

of 2-{2-[aryloxymethyl] phenyl}-[1,3]-thiazoles and the results of such studies are also included in this article.

Results and discussion

Chemistry

One series of target molecules 2-[2-(aryloxymethyl)phenyl]-4-phenyl-[1,3]-thiazoles **4a–p** were synthesized in good yield by the reaction of 2-(aryloxymethyl)benzothioamides **3a–d** with various phenacyl bromides in ethanol under reflux condition. The compounds **3a–d** were prepared by the reaction of 2-(aryloxymethyl)benzamides **2a–d** with phosphorous pentasulfide in tetrahydrofuran at 50 °C. The compounds **2a–d** were prepared from 2-(aryloxymethyl)benzoyl chlorides and aqueous ammonia. Another series of molecules, 2-[2-(aryloxymethyl)phenyl]-4-substituted-[1,3]-thiazoles **6a–l** by reaction of 4-chloromethyl-2-[2-(aryloxymethyl)phenyl]-[1,3]-thiazoles **5a–d** with various amines and phenols in the presence of potassium carbonate in methyl isobutyl ketone (MIBK). The compounds **5a–d** were synthesized in moderate yield by condensation of **3a–d** with 1,3-dichloroacetone in MIBK. All the compounds were characterized by analytical and spectroscopic data. The characterization data of compounds **4a–p** and **6a–l** are given in Tables 1 and 2.

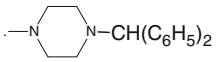
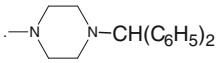
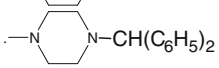
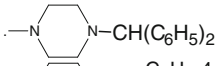
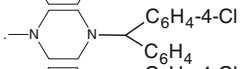
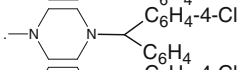
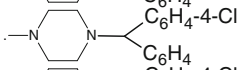
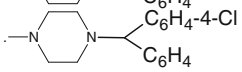
The formation of benzamides was confirmed by their elemental analysis, IR and NMR data. IR spectrum of **2a** showed absorption bands at 3298, 3127, 2980, 2876, 1666, 1611 and 1231 cm^{-1} for its $–NH_2$, ArC–H, CH_3, C=O, C=C and C–O groups, respectively. While, its ^1H NMR spectrum showed sharp singlet at δ 2.19 and δ 5.28 ppm due to ring A-CH_3 and OCH_2 protons, respectively. The four protons of ring A were resonated as two multiplets in the region δ 6.80–6.93 and δ 7.09–7.20 ppm. The aromatic protons of ring B appeared as a multiplet in the region δ 7.35–7.53 ppm where as and NH_2 proton appear two singlets at δ 7.57 and δ 7.88. In the 100 MHz, ^{13}C NMR spectrum of **2a** showed signals at δ 16.36 ppm, 67.45 ppm due to ring A-CH_3 and OCH_2 carbon atoms and peaks at δ 111.80 and 120.78 ppm (C_6 and C_3 of ring A), 126.46 and 127.38 ppm (C_5 and C_4 of ring A), 127.94 ppm (C_2 of ring B), 128.12 ppm (C_3 of ring B), 128.53 and 130.40 ppm (C_4 and C_5 of ring B), 130.92 (C_2 of ring A), 135.92 and 136.04 ppm (C_6 and C_1 of ring B), 156.80 ppm (C_1 of ring A) and 170.78 ppm (C=O group), respectively. The peaks at δ 16.36, 67.45, 111.80, 120.78, 126.83, 127.38, 127.94, 128.12, 128.53 and 130.40 ppm were observed in DEPT experiment. The other peaks at δ 130.92, 135.92, 136.04, 156.80 and 170.78 ppm due to quaternary carbon atoms were disappeared on DEPT experimentation.

The benzothioamide, **3a** showed IR absorption bands at showed IR absorption bands at 3394, 3266, 3101, 2918, 2867, 1589, 1411 and 1247 cm^{-1} for its $–NH_2$, ArC–H, CH_3, C=C, C=S and C–O groups, respectively. The presence of an absorption band at 1,411 cm^{-1} and disappearance of characteristic band due to C=O group at 1,666 cm^{-1} revealed the conversion of **2a–3a**. In the ^1H NMR spectrum, **3a** showed two singlets at δ 2.32 and 5.05 ppm for its ring A-CH_3 and OCH_2 protons, respectively. The 3,6-aromatic protons ring A appeared as two distinct doublets at δ 7.72 ($J = 7.05$ Hz) and δ 7.78 ppm ($J = 7.60$ Hz), where as 4,5-aromatic protons resonated as

Table 1 Characterization data of 4-aryl-[2-(aryloxymethyl)phenyl]-[1,3]thiazoles (**4a–p**)

Compd.	R	Ar	Molecular formula (MW)	MP (°C)	Yield (%)
4a	2-CH_3	3-$CONH_2$-4-OH-C_6H_3	$C_{24}H_{20}N_2O_3S$ (416.49)	158–160	85
4b	3-CH_3	3-$CONH_2$-4-OH-C_6H_3	$C_{24}H_{20}N_2O_3S$ (416.49)	150–152	82
4c	4-CH_3	3-$CONH_2$-4-OH-C_6H_3	$C_{24}H_{20}N_2O_3S$ (416.49)	145–146	78
4d	4-Cl	3-$CONH_2$-4-OH-C_6H_3	$C_{23}H_{17}ClN_2O_3S$ (436.91)	162–164	86
4e	2-CH_3	5-Cl-2-SO_2NH_2-3-thienyl	$C_{21}H_{17}ClN_2O_3S_3$ (477.01)	146–148	78
4f	3-CH_3	5-Cl-2-SO_2NH_2-3-thienyl	$C_{21}H_{17}ClN_2O_3S_3$ (477.01)	134–136	78
4g	4-CH_3	5-Cl-2-SO_2NH_2-3-thienyl	$C_{21}H_{17}ClN_2O_3S_3$ (477.01)	142–144	76
4h	4-Cl	5-Cl-2-SO_2NH_2-3-thienyl	$C_{20}H_{14}Cl_2N_2O_3S_3$ (497.43)	146–147	80
4i	2-CH_3	3-Br-C_6H_4	$C_{23}H_{18}BrNOS$ (436.36)	100–102	72
4j	3-CH_3	3-Br-C_6H_4	$C_{23}H_{18}BrNOS$ (436.36)	106–108	74
4k	4-CH_3	3-Br-C_6H_4	$C_{23}H_{18}BrNOS$ (436.36)	104–106	70
4l	4-Cl	3-Br-C_6H_4	$C_{22}H_{15}BrClNOS$ (456.86)	142–144	82
4m	2-CH_3	4-NO_2-C_6H_4	$C_{23}H_{18}N_2O_3S$ (402.46)	138–140	78
4n	3-CH_3	4-NO_2-C_6H_4	$C_{23}H_{18}N_2O_3S$ (402.46)	142–148	76
4o	4-CH_3	4-NO_2-C_6H_4	$C_{23}H_{18}N_2O_3S$ (402.46)	136–137	78
4p	4-Cl	4-NO_2-C_6H_4	$C_{22}H_{15}ClN_2O_3S$ (422.88)	156–158	82

Table 2 Characterization data of 4-aryl-[2-(aryloxymethyl)phenyl]-[1,3]thiazoles (**6a–l**)

Compd.	R	R′	Molecular formula (MW)	MP (°C)	Yield (%)
6a	2-CH_3		$C_{35}H_{35}N_3OS$ (545.73)	118–120	68
6b	3-CH_3		$C_{35}H_{35}N_3OS$ (545.73)	112–114	66
6c	4-CH_3		$C_{35}H_{35}N_3OS$ (545.73)	114–116	70
6d	4-Cl		$C_{34}H_{32}ClN_3OS$ (566.15)	124–126	72
6e	2-CH_3		$C_{35}H_{34}ClN_3OS$ (580.18)	136–138	74
6f	3-CH_3		$C_{35}H_{34}ClN_3OS$ (580.18)	132–133	71
6g	4-CH_3		$C_{35}H_{34}ClN_3OS$ (580.18)	130–132	70
6h	4-Cl		$C_{34}H_{31}Cl_2N_3OS$ (600.60)	128–130	72
6i	2-CH_3	4-ClC_6H_4O–	$C_{24}H_{20}ClNO_2S$ (421.93)	108–110	68
6j	3-CH_3	4-ClC_6H_4O–	$C_{24}H_{20}ClNO_2S$ (421.93)	110–112	72
6k	4-CH_3	4-ClC_6H_4O–	$C_{24}H_{20}ClNO_2S$ (421.93)	98–102	66
6l	4-Cl	4-ClC_6H_4O–	$C_{23}H_{17}Cl_2NO_2S$ (442.35)	118–120	70

two triplets at δ 6.97 and 7.13 ppm. The four aromatic protons of ring B resonated as multiplets in the region, δ 7.26–7.47. The NH_2 protons appeared as two distinct singlets at δ 9.60 and 10.06 ppm. ^{13}C NMR spectrum of **3a** showed signals at δ 21.56 ppm, 68.87 ppm for its ring A-CH_3 and OCH_2 carbon atoms. The other peaks observed are at δ 112.11 and 115.73 ppm (C_6 and C_3 of ring A), 117.80 and 122.04 ppm (C_5 and C_4 of ring A), 126.79 and 128.02 ppm (C_4 and C_5 of ring B), 128.96 and 129.96 ppm (C_3 and C_4 of ring B), 136.96 (C_2 of ring A), 139.47 and 143.37 ppm (C_6 and C_1 of ring B), 158.76 ppm (C_1 of ring A) and 202.62 ppm (C=S group), respectively.

Further, cyclization of **3d** to 2-[2-(4-chlorophenoxymethyl)phenyl]-4-(3-bromophenyl)-[1,3]-thiazole **4l** was confirmed from its IR spectrum, which showed absorption bands at 3078, 2984, 1698, 1591, 1070, 784 and 580 cm^{-1} for ArC–H, C–H, C=N, C=C, C–S, C–Cl and C–Br groups, respectively. The disappearance of characteristic absorption bands due to NH_2 group of **3d** clearly indicated its transformation to yield **4l**. The ^{1}H NMR spectrum of compound **4l** showed sharp singlet at δ 5.57 ppm for its OCH_2 protons and the aromatic protons ring A appeared as two distinct doublets at δ 6.90 ppm (J = 8.8 Hz) and δ 7.21 ppm (J = 8.8 Hz). The three aromatic protons of ring C appeared as a complex multiplet in the region δ, 7.23–7.27 ppm and a singlet at δ, 7.39 ppm for C_2-aromatic proton of ring C. Similarly, the 3,4-aromatic protons of ring B resonated as multiplet in the region δ 7.44–7.52 ppm and 2,6-protons resonated as distinct doublets at δ 7.75 and 7.80 ppm with J = 8.3 Hz and J = 8.1 Hz, respectively. The only one thiazole proton present in the molecule was resonated as a singlet at δ, 7.29. Further, ^{13}C NMR spectrum of **4l** manifested signals at δ, 68.77 ppm due to –OCH_2 and peaks at δ 114.13 ppm (C_2 and C_6 of ring A), 116.08 ppm (C_1 of ring C), 122.99 ppm (C_3 of ring C), 124.67 ppm (C_4 and C_5 of ring C), 125.74 ppm (C_4 of ring A), 128.13 and 128.54 ppm (C_2 and C_6 of ring C), 129.43 ppm (C_5 of thiazole), 129.82 ppm (C_3 and C_5 of ring A), 130.07 ppm (C_5 of ring B), 130.31 ppm (C_2 and C_3 of ring B), 131.14 ppm (C_4 of ring B), 135.29 ppm (C_6 of ring B), 136.22 ppm (C_1 of ring B), 154.47 ppm (C_4 of thiazole), 157.33 ppm (C_1 of ring A) and 167.31 ppm (C_2 of thiazole group), respectively. The peaks at δ, 68.77, 114.13, 116.08, 124.67, 128.13, 128.53, 129.39, 129.43, 129.82, 130.07, 130.31 and 131.14 ppm were observed in DEPT experiment. The other peaks at δ, 122.99, 125.74, 135.29, 136.22, 154.47, 157.33 and 167.31 ppm due to quaternary carbon atoms were disappeared on DEPT experimentation. Further, FAB MS spectrum showed the molecular ion peak at m/z 457 which corresponds to its molecular formula, $C_{22}H_{15}BrClNOS$.

The structure of **5d** was confirmed by its spectroscopic data. The IR spectrum showed absorption bands at 3104, 2990, 1674, 1578, 1194, 1072, 766 cm^{-1} for ArC–H, C–H, C=N, C=C, C–O, C–S and C–Cl groups, respectively. In the 1H NMR spectrum, **5d** showed singlets at δ 4.66 and 5.43 corresponding to CH_2 and OCH_2 protons, respectively. The aromatic protons ring A appeared as two

distinct doublets at δ 6.87 ppm ($J = 6.9$ Hz) and at δ 7.21 ppm ($J = 6.9$ Hz). The thiazole proton was resonated as a singlet at δ 7.30 ppm. The 3,4-aromatic protons ring B appeared as a triplet at δ 7.42 ppm ($J = 7.6$ Hz), where as 2,5-aromatic protons resonated as a doublet at δ 7.72 ppm ($J = 8.8$ Hz). In ^{13}C NMR spectrum, signals observed at δ, 41.0 and 68.55 ppm were assigned to CH_2 and $-OCH_2$ groups and peaks at δ 116.17 ppm (C_2 and C_6 of ring A), 118.07 ppm (C_5 of ring B), 125.71 ppm (C_4 of ring A), 128.15 ppm (C_3 of ring B), 128.58 ppm (C_2 of ring B), 129.34 ppm (C_5 of thiazole), 129.92 ppm (C_3 and C_5 of ring A), 130.11 ppm (C_4 of ring B), 131.29 ppm (C_1 of ring B), 135.37 ppm (C_6 of ring B), 152.86 ppm (C_4 of thiazole), 157.29 ppm (C_1 of ring A) and 167.72 ppm (C_2 of thiazole group), respectively. The FAB mass spectrum showed a protonated molecular ion peak at *m/z* 351, in agreement with its molecular formula, $C_{17}H_{13}Cl_2NOS$.

IR spectrum of compound **6h** reveals the presence of ArC–H, C–H, C=N, C=C, C–S and C–Cl by showing absorption bands at 3122, 2995, 1687, 1590, 1028 and 772, 765 cm^{-1}, respectively. The ^{1}H NMR spectrum showed a sharp singlets at δ 2.42, 2.59, 3.71, 4.20 and 5.41 ppm, which correspond to 2,6-piperazine protons, 3,5-piperazine protons, N–CH_2–N protons, CH and OCH_2 protons, respectively. The 2,6-aromatic protons of ring A resonated a doublet at δ 6.82 ppm ($J = 8.9$ Hz). The ring B 2,5-aromatic protons resonated as a triplet at δ 7.69 ($J = 8.8$ Hz). The remaining 3,5-aromatic protons of ring A, 3,4-aromatic protons of ring B, 4-chlorophenyl protons, phenyl protons and thiazole proton appeared as a complex multiplet in the range δ 6.13–7.47 ppm. Furthermore, ^{13}C NMR spectrum of **6h** manifested signals at δ 51.72, 53.28, 58.02, 68.47 and 75.48 ppm for 2,6 carbon of piperidine, 3,5 carbon of piperidine, $-CH_2$, $-OCH_2$ and CH carbons, respectively. The peaks at δ 116.01 ppm (C_2 and C_6 of ring A), 125.62 ppm (C_1 of ring B), 127.19 ppm (C_2 and C_6 of 4-Cl phenyl in ring C), 127.82 ppm (C_2 and C_6 of phenyl in ring C), 128.08 ppm (C_2 of ring B), 128.57 ppm (C_3 and C_4 of ring B), 128.61 ppm (C_5 of ring B), 128.67 ppm (C_5 of thiazole), 129.16 ppm (C_3 and C_5 of phenyl in ring C), 129.28 ppm (C_4 of phenyl in ring C), 129.73 ppm (C_3 and C_5 of 4-Cl phenyl in ring C), 130.0 ppm (C_3 and C_5 of ring A), 131.80 ppm (C_4 of ring A), 132.54 ppm (C_4 of 4-Cl phenyl in ring C), 135.09 ppm (C_1 of 4-Cl phenyl in ring C), 136.23 ppm (C_1 of phenyl in ring C), 141.33 ppm (C_6 of ring B), 142.12 ppm (C_4 of thiazole), 157.28 ppm (C_1 of ring A) and 166.57 ppm (C_2 of thiazole group), respectively. Furthermore, the structure of **6h** was also confirmed by recording its mass spectrum, which showed a molecular ion peak at *m/z* 600. The observed molecular mass is in agreement with the assigned molecular formula, $C_{34}H_{31}Cl_2N_3OS$.

Anti-inflammatory activity studies

The tested compounds showed anti-inflammatory activity ranging from 40.40 to 76.42 %, whereas standard drug diclofenac Na showed 75.93 % inhibition, after 3 h. The anti-inflammatory activity of 2-[2-(aryloxymethyl)phenyl]-4-phenyl-1,3-thiazoles **4a–p** is in the range of 40.40–76.42 %. The thiazole derivative **4h** having 4-chlorophenoxymethylphenyl and 5-chloro-2-sulfonamidophenyl groups attached to 4th position presented highest anti-inflammatory activity (76.42 %) better than the standard drug diclofenac Na. Other four compounds **4d–g** showed very significant activity. They contain 2-hydroxy-4-carboxamido-phenyl, 5-chloro-2-sulfonamidophenyl group on C-4 position. On the other hand, the remaining compounds exhibited moderate to good inhibition.

The anti-inflammatory activity of 2-[2-(aryloxymethyl)phenyl]-4-substituted-[1,3]-thiazole (**6a–l**) is in the range of 56.90–76.42 %. Compounds **6h** and **6l** showed the highest anti-inflammatory activity (76.42 %) better than the standard drug diclofenac Na. The good activity may be attributed to presence of *p*-chlorophenoxymethylphenyl and 4-chlorobenzhydryl piperazine and 4-chlorophenyl moieties attached to the thiazole nuclei. However, the remaining thiazoles possessed moderate to good activity.

Antimicrobial activity studies

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **4a–p** and **6a–l** showed moderate to good activity. The compounds **4d**, **4h**, **6d–h** and **6l** showed comparatively good activity against all the bacterial strains. The good activity may be attributed to presence of 4-chlorophenoxymethylphenyl and 2-hydroxy-4-carboxamidophenyl, 5-chloro-2-sulfonamidophenyl, 4-chlorobenzhydryl piperazine moieties attached to the thiazole nuclei. However, the compounds **4a–c**, **4e–g**, **4p**, **6a–c**, **6i–k** exhibited moderate activity compared to that of standard against all the bacterial strains.

The compounds **4d**, **4h**, **6d**, **6h** and **6l** showed comparatively good growth inhibition to all the fungal strains. The presence of 4-chlorophenoxymethylphenyl and 2-hydroxy-4-carboxamido-phenyl, 5-chloro-2-sulfonamidophenyl, 4-chlo robenzhydryl piperazine moieties attached to the thiazole ring may be responsible for their significant fungal growth inhibition. On the other hand, compounds **4a–c**, **4e–g**, **4p**, **6a–g** and **6i–k** exhibited moderate activity compared to that of standard against *C. albicans and A. niger*. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure–activity relationship and to optimize the effectiveness of this series of molecules.

NLO property

It is known from the literature that thiazoles and their derivatives are showing some interesting physical properties other than biological properties. The present study was primarily aimed at the development of a newer variety of NLO crystals. The preliminary SHG efficiency studies favours further study on development of single crystal and its optical properties. In addition, there are good chances of identifying entirely novel materials with promising properties. The SHG efficiency of the newly synthesized 2-{2-[aryloxymethyl]phenyl}-[1,3]-thiazoles **4a**–**p** is studied. The SHG measurement revealed that among the compounds tested **4e**, **4h**, **4l**, **4m**, **4o** and **4p** shown very low SHG value compared to urea. Interestingly, compound **4n** showed very good NLO property compared to other compounds and also the reference compound, urea. The compounds containing donor–acceptor groups in their structure exhibit good NLO property. The 4-nitrophenyl moiety and 3-methylphenoxymethyl moiety in the heteroaromatic system **4n** act as a strong electron acceptor and donor groups and thus enhancing its β value. It is evident from the powder SHG data that the compound **4n** is exhibiting 3.48 times higher SHG efficiency than urea, a well-known organic NLO material.

Conclusion

Several 2-[2-(aryloxymethyl)phenyl]-4-phenyl-[1,3]-thiazole (**4a**–**p**) and 2-[2-(aryloxymethyl)phenyl]-4-substituted-[1,3]-thiazole (**6a**–**l**) were synthesized in 60–70 % yields and were characterized by ^{1}HNMR, ^{13}C NMR, mass and IR spectral studies. All the newly synthesized compounds were screened for their anti-inflammatory, antibacterial and antifungal properties. Preliminary anti-inflammatory studies indicate that **4h**, **4d**–**h** and **6l** possess very good activity. However, further detailed studies on activity and long-term toxicity need to be carried out before any final conclusion can be drawn.

The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against pathogenic strains. Structure and biological activity relationship of title compounds showed that presence of *p*-chlorophenoxymethylphenyl group at position 2 and 2-hydroxy-4-carboxamido-phenyl, 5-chloro-2-sulfonamidophenyl, 4-chlorobenzhydryl piperazine and 4-chloro phenyl moieties attached to the position 4 of thiazole ring of the title compounds are responsible for good anti-inflammatory and antimicrobial activity. The screening data showed that the compounds have shown promising antibacterial and antifungal activities against the screened organisms. Therefore, it was concluded that there exists ample scope for further study in this class of compounds.

The SHG efficiency of the newly synthesized 2-4a–**p** are determined. Compound 2-{2-[(3-methylphenoxy)methyl] phenyl}-4-(4-nitrophenyl)-[1,3]-thiazole **4n** showed very good NLO property compared to other compounds and also the reference compound, urea. However, the remaining compounds did not show good NLO property.

Experimental

General techniques

Melting points were determined by the open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 4100 type A spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz NMR spectrometer/Perkin-Elmer EM300 MHz spectrometer using TMS as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 spectrophotometer/Data system using Argon/Xenon (6 kV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). The progress of the reaction was monitored by thin layer chromatography (TLC) on pre-coated silica gel G plates.

*General procedure for the preparation of 2-(aryloxymethyl)benzoic acids (Limban et al., 2008) (**1a**–**d**)*

Phthalide (15.0 g, 112 mmol), substituted phenols (23.6 g, 214 mmol) and sodium methoxide (47.6 g, 220 mmol) were suspended in 150 mL of *n*-butanol and stirred at 140 °C for 15 h and reaction completion was checked by TLC. The reaction mixture was cooled, 400 mL of water was added, and the mixture was acidified to pH 4 at 20 °C with concentrated hydrochloric acid. The product obtained was filtered, washed with water and dried. The crude product was recrystallized from methanol/water.

*2-(2-Methylphenoxymethyl)benzoic acid (**1a**)* Yield 75 %; colourless solid; m.p. 150–152 °C; IR (KBr, γ_{max}, cm^{-1}): 3438 (O–H), 3058 (ArC–H), 2898 (C–H), 1696 (C=O), 1240 (C–O); 1H NMR (400 MHz, DMSO, δ ppm): 2.22 (s, 3H, ring A-CH_3), 5.43 (s, 2H, –OCH_2), 6.84 (t, 1H, rings A–H, $J = 7.2$ Hz), 6.90 (d, 1H, rings A–H, $J = 7.2$ Hz), 7.12–7.17 (m, 2H, rings A–H), 7.44 (t, 1H, rings B–H, $J = 7.6$ Hz), 7.61 (t, 1H, rings B–H, $J = 7.6$ Hz), 7.69 (d, 1H, rings B–H, $J = 8.0$ Hz), 7.92 (d, 1H, rings B–H, $J = 8.0$ Hz), 13.08 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): δ 16.56 (ring A-CH_3), 68.03 (OCH_2), 111.61(C_6 of ring A), 120.70 (C_5 of ring A), 126.21(C_6 of ring B), 126.92 (C_4 of ring A), 127.09 (C_3 of ring A), 127.23 (C_2 of ring B), 128.22 (C_2 of ring A), 130.77 (C_5 of ring B), 131.75 (C_3 of ring B), 133.78 (C_4 of

ring B), 141.26 (C_1 of ring B), 156.69 (C_1 of ring A) and 172.80 (C=O).

*2-(4-Methylphenoxymethyl)benzoic acid (**1c**)* Yield 78 %; colourless solid; m.p. 126–128 °C; IR (KBr, γ_{max}, cm^{-1}): 3455 (O–H), 3078 (ArC–H), 2960 (C–H), 1685 (C=O), 1256 (C–O); ^{1}H NMR (400 MHz, DMSO, δ ppm): 2.38 (s, 3H, ring A-CH_3), 5.36 (s, 2H, –OCH_2), 6.75 (d, 2H, rings A–H, $J = 8.9$ Hz), 6.85 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.07–7.50 (m, 2H, rings B–H), 7.65–8.18 (m, 2H, rings B–H), 13.02 (s, 1H, OH).

*2-(4-Chlorophenoxymethyl)benzoic acid (**1d**)* Yield 80 %; colourless solid; m.p. 167–169 °C; IR (KBr, γ_{max}, cm^{-1}): 3440 (O–H), 3096 (ArC–H), 2948 (C–H), 1694 (C=O), 1236 (C–O), 748 (C–Cl); ^{1}H NMR (300 MHz, DMSO, δ ppm): 5.53 (s, 2H, –OCH_2), 6.93 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.26 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.44 (t, 1H, rings B–H, $J = 7.5$ Hz), 7.63 (t, 1H, rings B–H, $J = 7.5$ Hz), 7.77 (d, 1H, rings B–H, $J = 7.2$ Hz), 8.18 (d, 1H, rings B–H, $J = 7.2$ Hz), 13.10 (s, 1H, OH).

*General procedure for the preparation of 2-(aryloxy methyl)benzamides (Prakash et al., 2008) (**2a–d**)*

Phosphorus pentachloride (41.5 g, 0.199 mol) was slowly added in 5–6 lots to the solution of 2-(aryloxymethyl)benzoic acid (30 g, 0.133 mol) in dichloromethane (150 mL) contained in a 4-necked round bottom flask and the resulting solution was refluxed for 4 h. After completion of the reaction checked by TLC, excess solvent was distilled out under reduced pressure. The residue was cooled, dissolved in acetone (50 mL) and a solution of aqueous ammonia (200 mL) in acetone (50 mL) was added slowly at 0–5 °C. After maintaining the reaction mass for about half an hour at 10–15 °C, the solid mass was filtered, washed with water and dried. The crude product was recrystallised from methanol.

*2-(3-Methylphenoxymethyl)benzamide (**2b**)* Yield 88 %; colourless solid; m.p. 230–234 °C; IR (KBr, γ_{max}, cm^{-1}): 3318, 3124 (NH_2), 2978, 2884 (C–H), 1665 (C=O), 1604 (C=C), 1235 (C–O); ^{1}H NMR (300 MHz, DMSO, δ ppm): 2.32 (s, 3H, Ar–CH_3), 5.05 (s, 2H, OCH_2), 7.16–7.23 (m, 2H, rings A–H), 7.36–7.40 (m, 2H, rings A–H), 7.43–7.85 (m, 4H, rings B–H), 7.89 (s, 1H, NH_2), 7.98 (s, 1H, NH_2); *Anal*. calculated for $C_{15}H_{16}N_2O_2$: C, 70.29, H, 6.29, N, 10.93; found: C, 70.28; H, 6.20; N, 10.92.

*2-(4-Methylphenoxymethyl)benzamide (**2c**)* Yield 86 %; colourless solid; mp. 238–241 °C; IR (KBr, ν cm^{-1}): 3324, 3118 (NH_2), 2982, 2875 (C–H), 1668 (C=O), 1617 (C=C), 1240 (C–O); ^{1}H NMR (400 MHz, DMSO, δ ppm): 2.28 (s, 3H, Ar–CH_3), 5.56 (s, 2H, OCH_2), 6.74 (d, 2H, rings A–H, $J = 7.5$ Hz), 7.02 (d, 2H, rings A–H, $J = 7.5$ Hz), 7.39 (d, 1H, rings B–H, $J = 8.7$ Hz), 7.49 (d, 1H, rings B–H, $J = 7.8$ Hz), 7.78 (t, 1H, rings B–H, $J = 7.5$ Hz), 7.82 (t, 1H, rings B–H, $J = 7.5$ Hz), 7.89 (s, 1H, NH_2), 8.14 (s, 1H, NH_2); *Anal*. calculated for $C_{15}H_{16}N_2O_2$: C, 70.29, H, 6.29, N, 10.93; found: C, 70.22; H, 6.24; N, 10.96.

*2-(4-Chlorophenoxymethyl)benzamide (**2d**)* Yield 90 %; colourless solid; mp. 242–244 °C; IR (KBr, ν cm^{-1}): 3326, 3116 (NH_2), 2976, 2880 (C–H), 1658 (C=O), 1602 (C=C), 1235 (C–O), 758 (C–Cl); ^{1}H NMR (400 MHz, DMSO, δ ppm): 5.62 (s, 2H, OCH_2), 6.67 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.16 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.33–7.62 (m, 2H, rings B–H), 7.72 (d, 1H, rings B–H, $J = 7.8$ Hz), 7.92 (d, 1H, rings B–H, $J = 7.8$ Hz), 7.98 (s, 1H, NH_2), 8.10 (s, 1H, NH_2); *Anal*. calculated for $C_{14}H_{13}ClN_2O_2$: C, 60.77, H, 4.74, N, 10.12; found: C, 60.73; H, 4.70; N, 10.10; FAB MS: *m/z* : 276 (100 %, M^+).

*General procedure for the preparation of 2-(aryloxymethyl)benzothioamides (**3a–d**)*

To a solution of 2-(aryloxymethyl)benzamide (20 g, 0.089 mol) in tetrahydrofuran (50 mL) phosphorous pentasulfide (40 g, 0.18 mol) was slowly added at 50 °C over a period of 2 h. The resulting mixture was stirred at 50–55 °C for 2 h and reaction completion was checked by TLC and then quenched into ice-cold water. It was then extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, and distilled to get the thioamide. The crude as such was used for the next stage.

*2-(3-Methylphenoxymethyl)benzathiamide (**3b**)* Yield 78 %; colourless low melting solid; IR (KBr, γ_{max}, cm^{-1}): 3396, 3260 (NH_2), 3087 (ArC–H), 2913 (CH_3), 1582 (C=C), 1408 (C=S), 1244 (C–O).

*2-(4-Methylphenoxymethyl)benzathiamide (**3c**)* Yield 80 %; colourless low melting solid; IR (KBr, γ_{max}, cm^{-1}): 3390, 3264 (NH_2), 3098 (ArC–H), 2922 (CH_3), 1584 (C=C), 1412 (C=S), 1246 (C–O).

*2-(4-Chlorophenoxymethyl)benzathiamide (**3d**)* Yield 80 %; colourless solid; mp. 62–64 °C; IR (KBr, γ_{max}, cm^{-1}): 3398, 3260 (NH_2), 3090 (ArC–H), 2930 (CH_3), 1580 (C=C), 1414 (C=S), 1240 (C–O), 758 (C–Cl); ^{1}H NMR (400 MHz, DMSO, δ ppm): 5.48 (s, 2H, OCH_2), 6.76 (d, 2H, rings A–H, $J = 8.8$ Hz), 6.94 (d, 2H, rings A–H, $J = 8.8$ Hz), 7.36 (t, 2H, rings B–H), 7.62 (d, 1H, rings

B–H, $J = 8.4$ Hz), 7.84 (d, 1H, rings B–H, $J = 8.4$ Hz), 9.71 (s, 1H, NH_2), 10.14 (s, 1H, NH_2).

*General procedure for the synthesis of 4-substituted-2-[2-(aryloxymethyl)phenyl]-[1,3]-thiazoles (**4a–p**)*

An equimolar mixture of the appropriate thioamide (**3**) (0.01 mol) and phenacylbromide (0.01 mol) in ethanol (10 mL) was refluxed for 4 h. After completion of the reaction checked by TLC, the mixture was cooled to room temperature and the solid obtained was filtered. The crude product was recrystallized from ethanol. The characterization data of **4a–p** are given in Table 1.

*4-(3-Carboxamido-2-hydroxy-phenyl)-2-[(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4a**)* IR (KBr, ν cm^{-1}): 3428, 3128 (NH_2), 3078 (ArC–H), 2950 (C–H), 1654 (C=N), 1599 (C=C), 1185 (C–O), 1080 (C–S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.92 (s, 3H, ring A-CH_3), 5.61 (s, 2H, OCH_2), 6.82–6.97 (m, 4H, rings A–H), 7.11 (br.s, 2H, –NH_2), 7.46 (t, 2H, rings B–H, $J = 8.4$ Hz), 7.66 (br.s, 1H, rings C–H), 7.78 (d, 2H, rings C–H, $J = 8.8$ Hz), 7.93 (d, 1H, rings B–H, $J = 8.8$ Hz), 7.97 (d, 1H, rings B–H, $J = 8.8$ Hz), 8.39 (s, 1H, thiazole moiety), 12.76 (s, 1 H, OH rings C); LCMS: *m/z* 416 (M^+, 100 %).

*4-(3-Carboxamido-2-hydroxy-phenyl)-2-[(4-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4c**)* IR (KBr, ν cm^{-1}): 3420, 3124 (NH_2), 3081 (ArC–H), 2980 (C–H), 1689 (C=N), 1598 (C=C), 1195 (C–O), 1126 (C–S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.86 (s, 3H, ring A-CH_3), 5.56 (s, 2H, OCH_2), 6.76 (d, 2H, rings A–H, $J = 8.4$ Hz), 6.88 (d, 2H, rings A–H, $J = 8.4$ Hz), 7.05 (br.s, 2H, –NH_2), 7.40 (t, 2H, rings B–H, $J = 7.8$ Hz), 7.57–7.66 (m, 2H, rings B–H), 7.71 (br.s, 1H, rings C–H), 7.82 (d, 2H, rings C–H, $J = 8.8$ Hz), 8.21 (s, 1H, thiazole moiety), 12.67 (s, 1H, OH ring C).

*4-(3-Carboxamido-2-hydroxy-phenyl)-2-[(4-chlorophenoxymethyl)phenyl]-[1,3]-thiazole (**4d**)* IR (KBr, ν cm^{-1}): 3428, 3128 (NH_2), 3086 (ArC–H), 2970 (C–H), 1686 (C=N), 1590 (C=C), 1205 (C–O), 1088 (C–S), 784 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.45 (s, 2H, OCH_2), 6.86 (d, 2H, rings A–H, $J = 8.8$ Hz), 7.20 (d, 2H, rings A–H, $J = 8.8$ Hz), 7.31 (br.s, 2H, –NH_2), 7.46 (t, 2H, rings B–H, $J = 8.1$ Hz), 7.72 (br.s, 1H, rings C–H), 7.83 (d, 2H, rings C–H, $J = 8.4$ Hz), 7.99 (d, 1H, rings B–H, $J = 8.4$ Hz), 8.18 (d, 1H, rings B–H, $J = 8.4$ Hz), 8.42 (s, 1H, thiazole moiety), 12.58 (s, 1 H, OH of ring C); LCMS: *m/z* 438 (M^+, 100 %), 440 (M+2, 33 %).

*4-(5-Chloro-2-sulfonamido-thien-3-yl)-2-[(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4e**)* IR (KBr, γ_{max} cm^{-1}): 3384, 3112 (NH_2), 3074 (ArC–H), 2980 (C–H), 1698 (C=N), 1599 (C=C), 1198 (C–O), 1078 (C–S), 768 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.17 (s, 3H, ring A-CH_3), 5.25 (s, 2H, OCH_2), 6.31 (s, 2H, –SO_2NH_2), 6.86–6.95 (m, 4H, rings A–H), 7.10–7.16 (m, 2H, rings B–H), 7.22 (s, 1H, thiazole moiety), 7.27 (s, 1H, thioneyl moiety), 7.48–7.63 (m, 2H, rings B–H); LCMS: *m/z* 478 (M^+, 100 %), 480 (M+2, 34 %).

*4-(5-Chloro-2-sulfonamido-thien-3-yl)-2-[(4-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4g**)* IR (KBr, γ_{max} cm^{-1}): 3394, 3125 (NH_2), 3077 (ArC–H), 2989 (C–H), 1684 (C=N), 1592 (C=C), 1203 (C–O), 1065 (C–S), 766 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.23 (s, 3H, ring A-CH_3), 5.33 (s, 2H, OCH_2), 6.37 (s, 2H, –SO_2NH_2), 6.73–6.82 (m, 4H, rings A–H), 7.02 (s, 1H, thiazole moiety), 7.12 (s, 1H, thioneyl moiety), 7.23–7.36 (m, 2H, rings B–H), 7.38–7.52 (m, 2H, rings B–H); LCMS: *m/z* 478 (M^+, 100 %), 480 (M+2, 33 %).

*4-(5-Chloro-2-sulfonamido-thien-3-yl)-2-[(4-chlorophenoxymethyl)phenyl]-[1,3]-thiazole (**4h**)* IR (KBr, γ_{max} cm^{-1}): 3387, 3120 (NH_2), 3080 (ArC–H), 2985 (C–H), 1681(C=N), 1591 (C=C), 1188 (C–O), 1066 (C–S), 774 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.62 (s, 2H, OCH_2), 6.32 (s, 2H, –SO_2NH_2), 6.60 (d, 2H, rings A–H, $J = 8.8$ Hz), 6.68 (d, 2H, rings A–H, $J = 8.8$ Hz), 6.74 (s, 1H, thiazole moiety), 7.06 (s, 1H, thioneyl moiety), 7.12–7.27 (m, 2H, rings B–H), 7.32–7.44 (m, 2H, rings B–H); LCMS: *m/z* 498 (M^+, 100 %).

*4-(3-Bromophenyl)-2-[(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4i**)* IR (KBr, γ_{max} cm^{-1}): 3082 (ArC–H), 2990 (C–H), 1684 (C=N), 1596 (C=C), 1185 (C–O), 1065 (C–S), 585 (C–Br); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.90 (s, 3H, $ArCH_3$), 5.67 (s, 2H, OCH_2), 6.86–7.16 (m, 4H, rings A–H), 7.19 (s, 1H, rings C–H), 7.30–7.44 (m, 3H, rings C–H), 7.52 (d, 1H, rings B–H, $J = 8.2$ Hz), 7.61 (t, 2H, rings B–H, $J = 7.8$ Hz), 7.73 (d, 1H, rings B–H, $J = 8.4$ Hz), 7.82 (s, 1H, thiazole moiety).

*4-(4-Nitrophenyl)-2-[(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4m**)* IR (KBr, γ_{max} cm^{-1}): 3084 (ArC–H), 2960 (C–H), 1675 (C=N), 1594 (C=C), 1450 (NO_2), 1200 (C–O), 1170 (NO_2), 1078 (C–S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (s, 3H, $ArCH_3$), 5.55 (s, 2H, OCH_2), 6.78–6.84 (m, 3H, rings A–H), 7.18–7.26 (m, 1H, rings A–H), 7.48 (t, 2H, rings B–H, $J = 8.1$ Hz), 7.73 (d, 1H, rings B–H, $J = 8.8$ Hz), 7.78 (d, 1H, rings B–H, $J = 8.8$ Hz), 7.85 (s, 1H, thiazole moiety), 8.02 (d, 2H,

rings C–H, $J = 8.6$ Hz), 8.24 (d, 2H, rings C–H, $J = 8.5$ Hz); LCMS: *m/z* 402 (M^+, 100 %).

*4-(4-Nitrophenyl)-2-[(3-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4n**)* IR (KBr, γ_{max} cm^{-1}): 3092 (ArC–H), 2976 (C–H), 1692 (C=N), 1594 (C=C), 1455 (NO_2), 1188 (C–O), 1180 (NO_2), 1067(C–S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (s, 3H, $ArCH_3$), 5.57 (s, 2H, OCH_2), 6.78–6.84 (m, 3H, rings A–H), 7.18–7.26 (m, 1H, rings A–H), 7.46–7.52 (m, 2H, rings B–H), 7.50–7.52 (m, 2H, rings B–H), 7.74 (s, 1H, thiazole moiety), 8.02 (d, 2H, rings C–H, $J = 8.2$ Hz), 8.22–8.26 (m, 2H, rings C–H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.57 (ring A-CH_3), 68.76 (–OCH_2) 113.39, 116.67 (C_2 & C_6 of ring A), 121.83 (C_2 & C_6 of ring C), 124.17 (C_5 of ring A), 126.8 (C_3 & C_5 of ring C), 128.34 (C_4 of ring A), 129.14 (C_5 of thiazole), 129.63 (C_5 of ring B), 130.0 (C_3 of ring B), 130.31 (C_2 of ring B), 131.20 (C_4 of ring B), 135.31 (C_3 of ring A), 137.06 (C_6 of ring B), 140.0 (C_1 of ring B), 147.28 (C_4 of ring C), 153.65 (C_1 of ring C), 157.24 (C_4 of thiazole), 158.71 (C_1 of ring A), 167.86 (C_2 of thiazole).

*4-(4-Nitrophenyl)-2-[(4-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**4o**)* IR (KBr, γ_{max} cm^{-1}): 3080 (ArC–H), 2969 (C–H), 1698 (C=N), 1599 (C=C), 1515 (NO_2), 1195 (NO_2), 1180 (C–O), 1056 (C–S); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.37 (s, 3H, $ArCH_3$), 5.42 (s, 2H, OCH_2), 6.74 (d, 2H, rings A–H, $J = 8.5$ Hz), 7.02 (d, 2H, rings A–H, $J = 8.6$ Hz), 7.56–7.65 (m, 4H, rings B–H), 7.74 (s, 1H, thiazole moiety), 7.95 (d, 2H, rings C–H, $J = 8.4$ Hz), 8.18 (d, 2H, rings C–H, $J = 8.2$ Hz); LCMS: *m/z* 402 (M^+, 100 %).

*4-(4-Nitrophenyl)-2-[(4-chlorophenoxymethyl)phenyl]-[1,3]-thiazole (**4p**)* IR (KBr, γ_{max} cm^{-1}): 3088 (ArC–H), 2979 (C–H), 1684 (C=N), 1591 (C=C), 1515 (NO_2), 1190 (NO_2), 1185 (C–O), 1055 (C–S), 788 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.63 (s, 2H, OCH_2), 6.98 (d, 2H, rings A–H, $J = 7.8$ Hz), 7.26 (d, 2H, rings A–H, $J = 7.8$ Hz), 7.51–7.64 (m, 4H, rings B–H), 7.72 (s, 1H, thiazole moiety), 8.06 (d, 2H, rings C–H, $J = 8.2$ Hz), 8.23 (d, 2H, rings C–H, $J = 8.2$ Hz); LCMS: *m/z* 424 (M^+, 100 %), 426 (M+2, 33 %).

*General procedure for the preparation of 4-(chloromethyl)-2-[2-(aryloxymethyl) phenyl]-[1,3]-thiazoles (**5a–d**)*

An equimolar mixture of the appropriate 2-(aryloxymethyl)benzothioamide (**1**) (23 g, 0.066 mol) and 1,3-dichloroacetone (12.5 g, 0.099 mol) in MIBK (100 mL) was refluxed for 3 h. After completion of the reaction checked by TLC, it was quenched into water and organic layer was separated. It was then washed with water, dried over anhydrous sodium sulphate, and concentrated to residue under reduced pressure to get the title compounds.

*4-Chloromethyl-2-[2-(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**5a**)* IR (KBr, γ_{max} cm^{-1}): 3098 (ArC–H), 2969 (C–H), 1682 (C=N), 1591 (C=C), 1187 (C–O),1064 (C–S), 758 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.25 (s, 3H, $ArCH_3$), 4.68 (s, 2H, –CH_2Cl), 5.47 (s, 2H, O–CH_2), 6.77–6.79 (m, 1H, rings A–H), 6.84–6.88 (m, 2H, rings A–H), 7.26 (m, 1H, rings A–H), 7.33 (s, 1H, thiozole moiety), 7.45 (t, 2H, rings B–H, $J = 8.2$ Hz), 7.73–7.80 (m, 2H, rings B–H).

*4-Chloromethyl-2-[2-(3-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**5b**)* IR (KBr, γ_{max} cm^{-1}): 3108 (ArC–H), 2979 (C–H), 1688 (C=N), 1590 (C=C), 1189 (C–O),1058 (C–S), 755 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.22 (s, 3H, $ArCH_3$), 4.60 (s, 2H, –CH_2Cl), 5.43 (s, 2H, O–CH_2), 6.62–6.67 (m, 2H, rings A–H), 6.78–6.80 (m, 2H, rings A–H), 7.30 (s, 1H, thiozole moiety), 7.34 (t, 2H, rings B–H, $J = 8.2$ Hz), 7.56–7.68 (m, 2H, rings B–H).

*4-Chloromethyl-2-[2-(4-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**5c**)* IR (KBr, γ_{max} cm^{-1}): 3114 (ArC–H), 2994 (C–H), 1678 (C=N), 1575 (C=C), 1190 (C–O),1066 (C–S), 760 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.32 (s, 3H, $ArCH_3$), 4.70 (s, 2H, –CH_2Cl), 5.48 (s, 2H, O–CH_2), 6.86 (d, 2H, rings A–H, $J = 8.8$ Hz), 6.94 (d, 2H, rings A–H, $J = 8.9$ Hz), 7.28 (s, 1H, thiozole moiety), 7.37 (t, 2H, rings B–H, $J = 8.2$ Hz), 7.42 (d, 2H, rings B–H, $J = 8.8$ Hz).

*General procedure for the synthesis of 4-substituted-2-[2-(aryloxymethyl)phenyl]thiazoles (**6a–l**)*

An equimolar mixture of **5** (0.02 mol) and amines/phenols (0.02 mol) was refluxed in MIBK (25 mL) in the presence of potassium carbonate for 8–10 h. After completion of the reaction, reaction mass was quenched into water, organic layer was separated, and washed with water and dried over sodium sulphate. The organic layer was concentrated under vacuum and the solid obtained after cooling was filtered and recrystallized from ethanol. The characterization data of **6a–l** are given in Table 2.

*4-[4-(Diphenylmethyl)piperzin-1-yl]methyl-2-[2-(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole (**6a**)* IR (KBr, γ_{max} cm^{-1}): 3110 (ArC–H), 2990 (C–H), 1685 (C=N), 1590 (C=S), 1199 (C–O), 1038 (C–S); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.94 (s, 3H, $ArCH_3$), 2.27 (s, 4H, piperidine), 2.50 (s, 4H, piperidine), 3.56 (s, 2H, –NCH_2), 4.23 (s, 1H,

–CH), 5.42 (s, 2H, OCH_2), 6.52–7.49 (m, 10H, bi-phenyl moiety), 7.52–7.71 (m, 8H, ring A and rings B–H), 7.72 (s, 1H, thiozole moiety); LCMS: *m/z* 545 (M^+, 100 %).

4-[4-(Diphenylmethyl)piperzin-1-yl]methyl-2-[2-(3-methylphenoxymethyl)phenyl]-[1,3]-thiazole ***(6b)*** IR (KBr, γ_{max} cm^{-1}): 3113 (ArC–H), 2986 (C–H), 1682 (C=N), 1592 (C=C), 1190 (C–O), 1041 (C–S); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.57 (s, 3H, $ArCH_3$), 2.22 (s, 4H, piperidine), 2.41 (s, 4H, piperidine), 3.70 (s, 2H, -NCH_2), 4.19 (s, 1H, –CH), 5.43 (s, 2H, OCH_2), 6.14–7.08 (m, 10H, bi-phenyl moiety), 7.15–7.45 (m, 8H, ring A and rings B–H), 7.78 (s, 1H, thiozole moiety).

4-[4-(Diphenylmethyl)piperzin-1-yl]methyl-2-[2-(4-chlorophenoxymethyl)phenyl]-[1,3]-thiazole ***(6d)*** IR (KBr, γ_{max} cm^{-1}): 3115 (ArC–H), 2985 (C–H), 1692 (C=N), 1585 (C=C), 1170 (C–O), 1036 (C–S), 792 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.26 (s, 4H, piperidine), 2.33 (s, 4H, piperidine), 3.62 (s, 2H, –NCH_2), 4.38 (s, 1H, –CH), 5.54 (s, 2H, OCH_2), 6.05–6.97(m, 10H, bi-phenyl moiety), 7.22–7.59 (m, 8H, ring A and rings B–H), 7.88 (s, 1H, thiozole moiety); LCMS: *m/z* 567 (M^+, 100 %), 569 (M+2, 32 %).

4-[4-({4-Chlorophenyl}{phenyl}methyl)piperzin-1-yl]methyl-2-[2-(2-methylphenoxy-methyl)phenyl]-[1,3]-thiazole ***(6e)*** IR (KBr, γ_{max} cm^{-1}): 3118 (ArC–H), 2989 (C–H), 1690 (C=N), 1595 (C=C), 1190 (C–O), 1034 (C–S), 787 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.64 (s, 3H, $ArCH_3$), 2.42 (s, 4H, piperidine), 2.59 (s, 4H, piperidine), 3.71 (s, 2H, –NCH_2), 4.20 (s, 1H, –CH), 5.416 (s, 2H, OCH_2), 6.72–6.75(m, 4H, rings A–H), 7.04–7.47 (m, 9H, bi-phenyl moiety), 7.54 (s, 1H, thiozole moiety), 7.57–7.63 (m, 4H, rings B–H).

4-(4-Chlorophenoxy)methyl-2-[2-(2-methylphenoxymethyl)phenyl]-[1,3]-thiazole ***(6i)*** IR (KBr, γ_{max} cm^{-1}): 3110 (ArC–H), 2996 (C–H), 1684 (C=N), 1594 (C=C), 1188 (C–O), 1032 (C–S), 764 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.64 (s, 3H, $ArCH_3$), 5.34 (s, 2H, OCH_2), 5.46 (s, 2H, OCH_2), 6.75–7.11 (m, 4H, rings A–H), 7.35–7.64 (m, 4H, rings C–H), 7.69 (s, 1H, thiozole moiety), 7.75 (d, 1H, rings B–H, $J = 7.8$ Hz), 8.01–8.18 (t, 1H, rings B–H, $J = 7.5$ Hz), 8.22–8.32 (t, 1H, rings B–H, $J = 7.5$ Hz), 8.41–8.53 (d, 1H, rings B–H, $J = 7.8$ Hz); LCMS: *m/z* 421 (M^+, 100 %), 423 (M+2, 33 %).

4-(4-Chlorophenoxy)methyl-2-[2-(3-methylphenoxymethyl)phenyl]-[1,3]-thiazole ***(6j)*** IR (KBr, γ_{max} cm^{-1}): 3112 (ArC–H), 2990 (C–H), 1690 (C=N), 1581 (C=C), 1198 (C–O), 1037 (C–S), 762 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.52 (s, 3H, $ArCH_3$), 5.26 (s, 2H, OCH_2), 5.38 (s, 2H, OCH_2), 7.00 (d, 2H, rings A–H, $J = 7.2$ Hz), 7.26 (d, 2H, rings A–H, $J = 7.2$ Hz), 7.51–7.64 (m, 4H, rings C–H), 7.72 (s, 1H, thiozole moiety), 7.85 (d, 1H, **rings** B–H, $J = 7.8$ Hz), 8.09 (t, 1H, rings B–H, $J = 7.5$ Hz), 8.12 (t, 1H, rings B–H, $J = 7.5$ Hz), 8.18 (d, 1H, rings B–H, $J = 7.2$ Hz).

4-(4-Chlorophenoxy)methyl-2-[2-(4-chlorophenoxymethyl)phenyl]-[1,3]-thiazole ***(6l)*** IR (KBr, γ_{max} cm^{-1}): 3110b (ArC–H Stretch), 2999 (C–H), 1690 (C=N), 1595 (C=C), 1190 (C–O), 1036 (C–S), 742, 758 (C–Cl); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.14 (s, 2H, OCH_2), 5.39 (s, 2H, OCH_2), 6.79 (d, 2H, rings A–H, $J = 7.2$ Hz), 7.95 (d, 2H, rings A–H, $J = 7.2$ Hz), 7.11–7.28 (m, 4H, rings C–H), 7.35 (s, 1H, thiozole moiety), 7.45 (d, 2H, rings B–H, $J = 7.8$ Hz), 7.73 (d, 2H, rings B–H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 66.43 (CH_2), 68.64(–OCH_2), 116.13 (C_2H and C_6H of ring A), 116.15 (C_2H and C_6H of ring C), 117.18 (C_5H of ring B), 125.73 (C_4H of ring A), 126.16 (C_4H of ring C), 128.27 (C_2H of ring B), 128.85 (C_5H of thiazole),129.33 (C_3H and C_5H of ring A), 129.44 (C_3H and C_5H of ring C), 130.03(C_3 of ring B), 130.08(C_4 of ring B), 131.54 (C_1H of ring B), 135.16 (C_6H of ring B), 152.80 (C_4H of thiazole), 156.98(C_1H of ring C), 157.31 (C_1H of ring A) and 167.47 (C_2 of thiazole group), respectively. LCMS: *m/z* 442 (M^+, 100 %).

Biological activity

Preliminary screening for anti-inflammatory activity

The in vivo anti-inflammatory activity of all the newly synthesized compounds was evaluated by carrageenan-induced rat paw oedema method (Winter *et al*., 1962). Wister albino rats of either sex weighing 180–250 g were used for the experiment. The compounds were tested at 10 mg/kg oral dose and were compared with the standard drug diclofenac Na at the same oral dose. The results were expressed as % inhibition of oedema over the untreated control group in Table 3.

Preliminary screening for antimicrobial activity

The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm (Bauer *et al*., 1996). All the compounds, **4a–p** and **6a-l**, were screened in vitro at a concentration of 10 μg/disc for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* and *Bacillus subtilis)* and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Antifungal evaluation was also carried out against *Candida albicans* and *Aspergillus niger* at a

concentration of 10 μg/disc. Standard antibacterial drug ciprofloxacin (10 μg/disc) and antifungal drug fluconazole (10 μg/disc) were also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The antibacterial activity was classified as highly active (≥26 mm), moderately active (11–25 mm), and least active (<11 mm). The results of antibacterial and antifungal activities are expressed in terms of zone of inhibition and presented in Table 4.

NLO property

The SHG measurement was made in accordance with the classical powder method developed by Kurtz and Perry using DCR-11 type Nd: YAG laser of power 4 mJ/pulse was used as source (Kurtz and Perry, 1968). A fundamental wave with a pulse width of 8 ns, repetition frequency 10 Hz, and a wavelength 1064 nm was applied to the upgraded microcrystalline powder samples with average particle size 100–150 μm densely loaded to glass capillary. The second harmonic wave of 532 was generated from the sample was detected by a photomultiplier (Hamamatsu-R 2059) as reflected light. The converted electrical signal was displayed on an oscilloscope (Tektronix-TDS 3000B). The signals amplitude in volts indicates the SHG efficiency of the compound. Comparison of relative SHG intensities was made with that of urea and data of thiazoles are given in Table 5.

Table 3 Antiinflammatory activity data of compounds (**4a–p**) and (**6a–l**)

Compd.	Dose (mg/kg body weight, p.o)	Increase in paw volume in mL (mean ± SEM)	% Inhibition of paw oedema
4a	10	0.0964 ± 0.0027	40.52
4b	10	0.0925 ± 0.0033	42.91
4c	10	0.0896 ± 0.0035	46.68
4d	10	0.0458 ± 0.0028	72.21
4e	10	0.0484 ± 0.0023	70.12
4f	10	0.0538 ± 0.0027	66.80
4g	10	0.0508 ± 0.0071	68.65
4h	10	0.0382 ± 0.0032	76.42
4i	10	0.0966 ± 0.0040	40.40
4j	10	0.0896 ± 0.0035	46.68
4k	10	0.0899 ± 0.0027	44.51
4l	10	0.0925 ± 0.0033	42.91
4m	10	0.0896 ± 0.0035	46.68
4n	10	0.0896 ± 0.0035	46.68
4o	10	0.0698 ± 0.0041	56.90
4p	10	0.0533 ± 0.0017	67.12
6a	10	0.0584 ± 0.0031	63.98
6b	10	0.0581 ± 0.0260	64.12
6c	10	0.0585 ± 0.0021	63.92
6d	10	0.0568 ± 0.0025	64.92
6e	10	0.0597 ± 0.0023	63.15
6f	10	0.0606 ± 0.0029	62.58
6g	10	0.0698 ± 0.0041	56.90
6h	10	0.0382 ± 0.0032	76.42
6i	10	0.0565 ± 0.0020	65.12
6j	10	0.0523 ± 0.0084	67.70
6k	10	0.0508 ± 0.0071	68.65
6l	10	0.0382 ± 0.0032	76.42
Control	0.1 mL/kg	–	–
Standard	10	0.0390 ± 0.0026	75.93

Diclofenac Na is used as the standard: $N = 6$ in each group. Carboxy methyl cellulose as a suspending agent

Table 4 Antibacterial activity data of compounds (**4a–p**) and (**6a–l**)

Compd.	Zone of inhibition in mm					
	Antibacterial activity				Antifungal activity	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
4a	18	18	20	21	16	18
4b	22	22	20	22	18	11
4c	20	20	19	20	20	18
4d	28	26	28	24	27	25
4e	22	20	20	22	18	16
4f	18	16	20	18	19	18
4g	20	18	22	20	20	16
4h	28	28	26	24	26	24
4i	10	12	08	08	10	11
4j	12	10	10	10	14	16
4k	10	12	08	10	14	11
4l	22	20	22	18	20	18
4m	10	12	14	10	12	14
4n	08	12	11	10	09	08
4o	12	10	10	12	11	14
4p	22	18	22	18	20	18
6a	23	23	20	18	09	08
6b	19	20	22	20	10	11
6c	20	21	18	18	10	08
6d	28	26	28	26	28	24
6e	28	28	26	24	22	20
6f	28	28	27	25	20	18
6g	28	28	28	24	20	19
6h	27	26	28	26	28	25
6i	20	18	22	20	20	16
6j	24	22	20	18	22	18
6k	22	19	24	17	20	18
6l	28	27	26	24	26	24
Ciprofloxacin	26	26	28	25	–	–
Flucanazol	–	–	–	–	26	25

Table 5 SHG conversion efficiency data of thiazoles (**4a–p**)

Compd.	SHG (X urea)
4a	–
4b	–
4c	–
4d	–
4e	2.3
4f	–
4g	–
4h	1.52
4i	–
4j	–
4k	–
4l	1.35
4m	1.6
4n	216
4o	3.6
4p	4.5
Urea	62

The SHG conversion efficiency of the sample is given by the formula:

Relative efficiency, $\eta = I_s/I_u$,

where I_s and I_u are the intensities at frequency $2_{(1)}$ transmitted through the same thickness of the sample and urea, respectively. The laser power was measured using a power meter. The laser used in the present experiment was Nd: YAG and the power were 13 mJ/s.

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