doi.org/10.36721/PJPS.2021.34.4.REG.1415-1420.1

New series of hydrazinyl thiazole derivatives of piperidin-4-one: Synthesis, structural elucidation, analgesic activity and comparative structure activity relationship

Rubina Siddiqui[1]*, Shamim Akhtar[2], Shazia Haider[1], Zafar Saied Saify[3], Mahwish Akhtar[4] and Sana Shamim[4]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Pakistan
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[3]HEJ Research Institute of Chemistry, University of Karachi, Karachi, Pakistan
[4]Dow College of Pharmacy, Dow University of Health Sciences, Karachi, Pakistan

Abstract: Seven new hydrazinyl thiazole derivatives of piperidin-4-one (PE3-PE9) have been synthesized by cyclization of intermediate thiosemicarbazone derivative (PE2). Parent molecule (PE1) was synthesized by one pot total synthesis using Mannich condensation reaction. Percent yield of most of the compounds found in between 70-85%. Compounds were identified by spectroscopic analysis. *In vivo* analgesic activity was examined using tail flick method. one-way ANOVA was used to compare the mean latency time of synthesized derivatives with control and standard. Analgesic activity was discussed in terms of structural differences between compounds. Among all the derivatives thiosemicarbazone derivative showed good analgesic activity (195.24%). Methoxy (-OCH_3) and bromo (-Br) containing thiazole derivative also showed good pain reducing property (167.62%, 203%) at a dose of 30mg/kg.

Keywords: Piperidin-4-one, hydrazinyl thiazole derivatives, analgesic activity, tail flick method.

INTRODUCTION

For the access of wide variety of biologically active functionalized molecule synthesis of heterocycles plays an important role in medicinal chemistry. Presence of heteroatoms change the electronic properties of molecule allow to optimize pharmacokinetics as well as pharmacodynamics properties of chemical entities. Currently, more than 75% of drugs used in medicine comprise heterocycles (Jampilek, 2019, Щекотихин, 2020). Among the heterocycles nitrogen containing or various combination of nitrogen atom with sulphur and oxygen in five and six membered ring considered as privilege structure. Since many decades heterocyclic thiazole, having nitrogen and Sulphur atoms have been explored for their activities such as antioxidant, antimicrobial, antitumor, anti-inflammatory, anticoagulant and anti-HIV (Espinosa, Zamora *et al*., 2003, Mohareb, Wardakhan *et al*., 2019, Ramalingam and Sarvanan, 2020, Rashdan, Abdelmonsef *et al*., 2020, Rawal, Tripathi *et al*., 2008, Sayed, Ali *et al*., 2019). An alicyclic nitrogen containing molecule piperidine is also present in natural and pharmaceutically active compounds possessing analgesic, antihypertensive antiviral, antimicrobial and central nervous system depressant activities (Mochizuki, Nakamoto *et al*., 2008, Pandey and Chawla, 2012, Shen, Yang *et al*., 2017). Phenyl piperidine such as meperidine, fentanyl and sufentanil have been used as analgesic agents over the past five decades(Elbaridi, Kaye *et al*., 2017, Kugita, Oine *et al*., 1965, Vardanyan and Hruby, 2014).

Chronic and acute pain management is one of the most prevalent public health issue world wise, current available drugs have unwanted side effects the most serious include gastrointestinal bleeding and perforation, platelet and renal dysfunctions (Hanlon, Guay *et al*., 2005, O'Neil, Hanlon *et al*., 2012, Piotrowska, Leppert *et al*., 2019, Power, 2011). Therefore, it is need to develop analgesic that provide more effective treatment and have reduced side effects, in this context we have synthesized seven phenyl piperidine hydrazinyl thiazole derivatives (Siddiqui, Akhter *et al*., 2019) as analgesic agents. These compounds showed potential to reduce the pain. In continuation of our previous research, in current study by using the same methodology we have developed new derivatives having same pharmacophore with small modification in the structure. Compounds were evaluated for analgesic activity by using tail flick method.

MATERIALS AND METHODS

Analytical grade solvents and all reagents were purchased from Merck and TCI (Japan). Kieselgel TLC plate was used for monitoring the synthesis process and checking of purity of compounds. Buchi 434 instrument was used for melting point determination. Shimadzu UV-1600 spectrophotometer, JASCO Fourier transformed infrared spectrophotometer were used for ultra violet and infrared spectrum of compounds respectively. JEOL and MAT112 were used for mass spectrum. ^{1}HNMR spectrum was obtained from Bruker AM300 at 300 and 500MHz.

**Corresponding author:* e-mail: rsiddiqui@uok.edu.pk

Synthesis

The novel hydrazinyl thiazole derivatives (PE3-PE9) have been synthesized by using 2-(3-methyl-2,6-diphenylpiperidin-4-ylidene) hydrazinecarbo-thioamide (PE2) which was prepared from 3-methyl-2,6-diphenyl piperidin-4-one (PE1) in three step procedure. The method of synthesis was already reported by our group (Siddiqui *et al*., 2019) only difference is instead of methyl isopropyl ketone, ethyl methyl ketone was used as shown in scheme -1.

Synthesis and Characterization of 3-methyl-2,6-diphenyl piperidin-4-one (PE1)

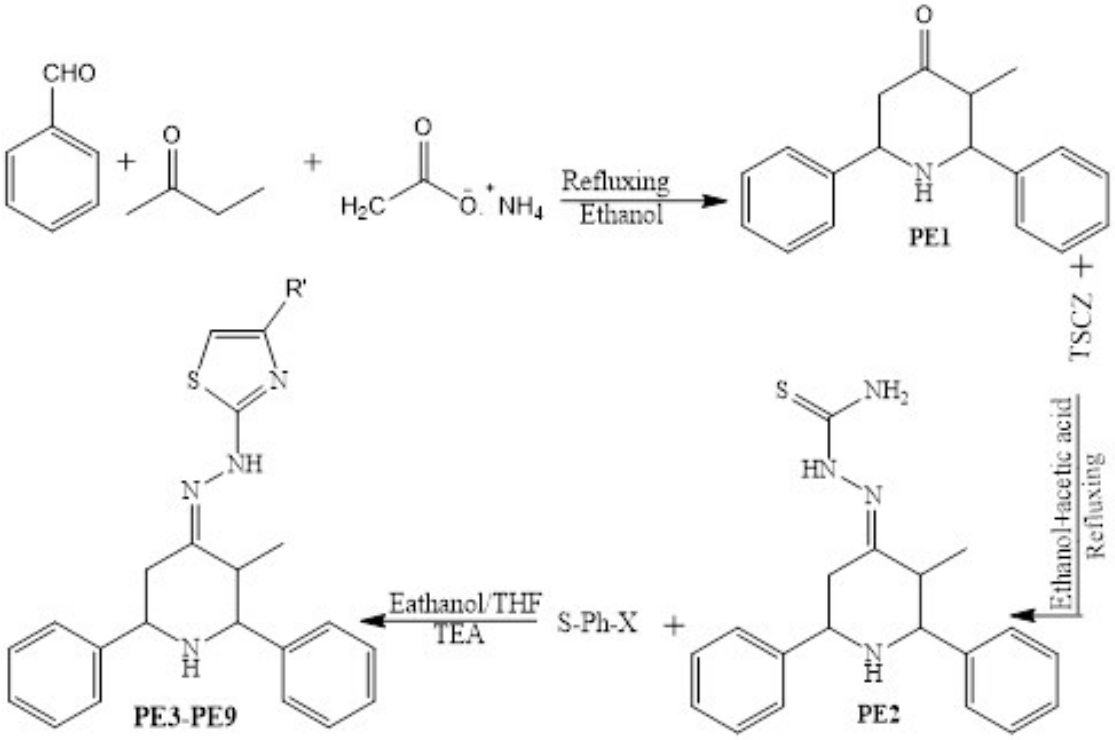
Parent compound 3-methyl 2,6-diphenylpiperidin-4-one was synthesized by refluxing the mixture of ethyl methyl ketone (0.01mol), benzaldehyde (0.02 mol) and dried ammonium acetate (0.01mol) in absolute ethanol (50ml). After completion of reaction, concentrated hydrochloric acid (5ml) was added, the obtained precipitates were suspended in acetone, the solution was made alkaline with the addition of aqueous ammonia; free base was precipitated out with addition of excess cold water in solution. Product purity was checked with TLC using mixture of ethyl acetate and hexane (3:7) (Scheme 1).

$C_{18}H_{19}NO$; %yield: 92; m.p: 112±01; $UV_{\lambda max}$(MeOH) nm: 204, 251, 256, 263; $IR\upsilon_{max}$(KBr) cm^{-1}: 2937, 2821, 1701, 1579, 1135, 862; EIMS m/z (%): 265.2 M^+ (81.6), 208.1(12.1), 194.1(69.6), 132.1(31.7), 118.1(18.9), 104.1(100.0); ^{1}H-NMR (DMSO, 300MHz) δ(ppm): 0.670-0.648 (d, *J*= 6.6 Hz, 4H, H-13), 2.493-2.396 (m, 3H ,H- 5b), 2.766-2.671 (m, 4H, H-1, 5a), 3.601-3.553 (m, 5H, H-3), 4.017-3.983 (d, *J*=10.2 Hz, 2H, H-2), 4.057-4.035 (t, 3H, H-6), 7.482 -7.219 (m, 10, H-8, 9, 10, 11, 12, 16, 17, 18, 19, 20).

Synthesis and Characterization of (Z)-2-(3-methyl-2,6-diphenylpiperidin-4-ylidene) hydrazinecarbo-thioamide (PE2)

Carbo-thioamide derivative was prepared by reflexing a mixture of 3-methyl 2,6-diphenylpiperidin-4-one (0.01 mol) and thiosemicarbazide (0.01 mol) for three hours with continuous stirring on hot plate in absolute ethanol (50 ml) containing few drops of glacial acetic acid. Progress of reaction was monitored by using TLC. Precipitate of product was obtained by pouring content of flask in ice cold water. The product washed with cold water and re-crystallized from absolute ethanol (Scheme 1).

$C_{19}H_{22}N_4S$; %yield: 86.5; m.p: 152±01; $UV_{\lambda max}$ (MeOH)nm: 205, 272; $IR\upsilon_{max}$(KBr) cm^{-1}: 3421, 3179, 2911, 1568, 1464, 1128; EIMS m/z (%): 338.1 M^+ (55.8), 263.1(50.6), 194.1(99.5), 158.1(31.7), 1144.1 (55.7), 106.1(80.0);^{1}H-NMR ($CDCl_3$, 300MHz) δ(ppm): 0.788-0.766 (d, *J*= 6.3 Hz, H-13), 2.496-2.485 (m, 3H, H-5b), 2.503-2.496 (m, 3H, H-1, 5a), 3.327 (s, 1H, H-2), 3.842-3.738 (t, 3H, H-6), 7.528-7.216 (m, 10rH, H-8, 9, 10, 11,



Where, TSCZ= Thiosemicarbazide, S-Ph-X= Substituted phenacyl halides, R' = 4-Cl-phenyl, 4-NO_2-phenyl, 3-NO_2-phenyl, 4-Br-phenyl, 4-OCH_3-phenyl, naphthalene,3,4-dihydoxy phenyl

12,19 20, 21, 22, 23), 8.096 (s, 2H, H-24), 10.530 (s, 1H, H-15).

General method for the synthesis of hydrazinyl thiazole derivatives of Piperidin-4-one (PE3-PE9)

Equimolar amount of 2-(3-methyl-2,6-diphenylpiperidin-4-ylidene) hydrazine carbo-thioamide (PE2) (0.01 mol) and substituted phenacyl halide (0.01 mol) were refluxed in ethanol/ THF (30 ml) containing 2-3 drops of tri-ethyl amine (TEA). After completion of reaction the content of reaction flask was poured onto ice water the obtained precipitates were filtered, washed from cold water and vacuum dried. The product recrystallized from hot ethanol (Scheme 1).

Characterization of (Z)-4-(4-chlorophenyl)-2-(2-(3-methyl-2,6-diphenylpiperidin-4-ylidene) hydrazinyl) thiazole (PE3)

$C_{27}H_{25}ClN_4S$; %yield: 85; m.p: 215±06; $UV_{\lambda max}$ (MeOH)nm: 202, 250, 273; $IR\upsilon_{max}$(KBr)cm^{-1}: 3432, 2956, 1576, 1420, 1019, 800, 643; EIMS m/z (%): 472.3 M^+ (31.7), 367(11.4), 312(21.2), 263(13.9), 205(33.3), 194(100);^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 2.338-2.290 (m, 3H, H-13b), 0.962-0.949 (d, *J*= 6.5 Hz, 4H, H-20), 2.631-2.598 (m, 4H, H-11,13a), 2.994-2.961 (m, 5H, H-9), 3.570-3.550 (d, *J*=10 Hz, 2H, H-10), 3.945-3.918 (m, 4H, H-12), 6.80 (s, 1H, H-5), 7.674-7.240 (m, 12H, H-16, 18, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32), 7.691-7.688 (d, *J*= 1.8 Hz, 2H, H-15,19), 10.643(s, 1H, H-6).

Characterization (Z)-2-(2-(3-methyl-2,6-diphenyl piperidin-4-ylidene)hydrazinyl)-4-(3-nitrophenyl) thiazole (PE4)

$C_{27}H_{25}N_5O_2S$;%yield: 69; m.p:175±0.3; $UV_{\lambda max}$ (MeOH) nm: 202, 237, 271; $IR\upsilon_{max}$(KBr) cm^{-1}: 3409, 3027, 2962, 1589, 1423, 1176; EIMS m/z (%): 483.3 M^+ (28.4), 451(4.8), 378(29.4), 323(13.3), 259 (10.8), 221(16.8), 194(100); ^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm):^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.901-0.894 (d, *J*=3.5 Hz, 4H, H-20), 2.425-2.418 (m, 3H, H-13b), 2.68-2.648 (m, 4H, H-11, 13a), 2.892-2.879 (m, 5H, H-9), 3.365-3.361 (d, *J*= 2 Hz, 2H, H-10), 3.954-3.935 (t, 4H, H-12), 7.240 (s, 1H, H-5), 7.418-7.362 (m, 10H, H-22, 23, 24, 25, 26, 28, 29, 30, 31, 32), 7.497 (t, 3H, H-18), 8.210-8.198 (d, *J*= 6 Hz, 2H, H-19), 8.371-8.368 (d, *J*=1.5 Hz, 2H, H-17), 8.574(s, 1H, H-15), 10.832 (s, 1H, H-6).

Characterization of (Z)-2-(2-(3-methyl-2,6-dipheny lpiperidin-4-ylidene)hydrazinyl)-4-(4-nitrophenyl) thiazole (PE5)

$C_{27}H_{25}N_5O_2S$; %yield: 75.5; m.p: 210±04; $UV_{\lambda max}$ (MeOH)nm: 204, 257, 295; $IR\upsilon_{max}$ (KBr) cm^{-1}: 3439, 2786, 1586, 1424, 1153; EIMS m/z (%): 483.2 M^+ (47.3), 466(10.8), 378(35.7), 323(22.4), 221 (12.2), 194(100);^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.898-0.892 (d, *J*= 3 Hz, 4H, H-20), 2.421-2.413 (m, 3H, H-13b), 2.684-2.627 (m, 4H, H-11, 13a), 2.875-2.857 (m, 5H, H-9), 3.364-3.338 (d, *J*= 13 Hz, 2H, H-10), 3.917-3.904 (m, 4H, H-12), 7.305 (s, 1H, H-5), 7.542-7.493 (m, 12H, H-15, 19, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32), 7.682-7.675 (d, *J*= 3.5 Hz, 2H, H-16, 18), 11.206 (s, 1H, H-6).

Characterization of (Z)-4-(4-bromophenyl)-2-(2-(3-methyl-2,6-diphenylpiperidin-4-ylidene)hydrazinyl) thiazole (PE6)

$C_{27}H_{25}BrN_4S$;%yield: 85.3; m.p:215±0.1; $UV_{\lambda max}$ (MeOH) nm: 203, 252, 274; $IR\upsilon_{max}$(KBr) cm^{-1}: 3396, 3153, 2931, 1582, 1417, 1092; EIMS m/z (%): 516.3 M^+ (27.7), 411(25), 378(16.9), 356(23.7), 324 (18.6), 254(53.3), 194(100); ^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.976-0.968 (d, *J*= 4 Hz, 4H,H-20), 2.410-2.389 (m, H, H-13b), 2.701-2.697 (m, 4H, H-11, 13a), 2.876-2.872 (m, 5H, H-9), 3.358-3.349 (d, *J*= 4.5 Hz, 2 H, H-10), 3.875-3.869 (t, 4H, H-12), 7.241 (s, 1H, H-5), 7.561-7.532 (m, 12H, H-16, 18, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32), 7.767-7.759(d, *J*= 4 Hz, 2H, H-15,19), 10.830 (s, 1H, H-6).

Characterization of (Z)-4-(4-methoxyphenyl)-2-(2-(3-methyl-2,6-diphenylpiperidin-4-ylidene)hydrazinyl) thiazole(PE7)

$C_{28}H_{28}N_4OS$; %yield: 67;m.p:180±06; $UV_{\lambda max}$(MeOH) nm: 202, 259; $IR\upsilon_{max}$(KBr) cm^{-1}: 3435, 3037, 2902, 1582, 1417, 1128; EIMS m/z (%): 468.2 M^+ (28.9), 449(14.9), 391(18.2), 363(14.7), 308(21.7), 259(27.3), 222(1105), 206(49.8), 194(100);^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.952-0.945 (d, *J*= 3.5 Hz, 4H, H-20), 2.521-2.510 (m, 3H, H-13b), 2.732-2.684 (m, 4H, H-11,13a), 2.784-2.754 (m, 5H, H-9), 3.542-3.514 (d, *J*=14 Hz, 2H, H-10), 4.032-4.027 (t, 4H, H-12), 7.021-6.997(d, *J*=12 Hz, 2H, H-16,18), 7.469-7.285 (m, 9H, H-23, 24, 25, 28, 29, 30, 31, 32, 5), 7.457-7.443 (d, *J*= 7 Hz, 2H, H-22, 26), 7.572-7.561 (d, *J*= 5.5 Hz, 2H, H-15, 19), 10.857 (s, 1H, H-6).

Characterization of (Z)-2-(2-(3-methyl-2,6-dipheny lpiperidin-4-ylidene)hydrazinyl)-4-naphthalen-2-yl) thiazole (PE8)

$C_{31}H_{28}N_4S$; % yield: 59 ;m.p:182±02; $UV_{\lambda max}$ (MeOH)nm: 217, 246 285; $IR\upsilon_{max}$(KBr) cm^{-1}: 3445, 2982, 1582, 1416, 1051;EIMS m/z (%): 488.2 M^+ (25), 411(25), 398(82.1), 361(25), 293(12.4), 278(10.4), 225(16.7), 210(36.5), 194(100); ^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.965-0.957 (d, *J*= 4 Hz, 4H, H-24), 2.512-2.485 (m, 3H, H-13b), 2.762-2.754 (m, 4H, H-11,13a), 2.964-2.952 (m, 5H, H-9), 3.854-3.847 (d, *J*= 3.5 Hz, 2H, H-10), 7.387-7.345 (m, 9H, H-27, 28, 29, 32, 33, 34, 35, 36, 5), 4.116-4.084 (t, 4H, H-12), 7.452-7.397 (d, *J*= 27.5 Hz, 2H, H-26, 30), 7.895-7.887 (m, 4H, H-21, 22), 8.034-8.012 (m, 4H, H-18, 19, 20, 23), 8.654 (s, 1H, H-15), 11.021(s, 1H, H-6).

Characterization of (Z)-4-(2-(2-(3-methyl-2,6-diphenyl piperidin-4-ylidene) hydrazinyl)thiazol – 4-yl)benzene-1,2-diol(PE-9)

$C_{27}H_{26}N_4O_2S$; % yield: 84;m.p:205±04; $UV_{\lambda max}$

Table 1: Analgesic potential of compound PE1-PE9 at 15 mg/kg in comparison with control and standard

Comp.	Dose	Latency time (seconds)						
		0min	30 min	60 min	90 min	120 min	150 min	180 min
PE1	15mg/kg	0.94±0.03 *(*)	1.37±0.03 **(**)	1.43±0.02 **(**)	1.21±0.06 **(**)	1.06±0.06 **(**)	1.03±0.03 **(**)	0.96±0.02 **(**)
PE2		0.80±0.04 **(**)	1.18±0.05 **(**)	1.91±0.05 **(*)	2.15±0.22 *(*)	1.84±0.12 *(**)	1.42±0.05 **(**)	1.01±0.03 **(**)
PE3		0.84±0.05 *(**)	1.14±0.07 **(**)	1.57±0.10 **(**)	1.92±0.13 *(**)	1.69±0.06 **(**)	1.34±0.09 **(**)	1.03±0.03 **(**)
PE4		0.85±0.04 *(**)	1.28±0.03 *(**)	1.62±0.14 **(**)	1.84±0.23 **(**)	1.55±0.13 **(**)	1.19±0.12 **(**)	0.98±0.04 **(**)
PE5		0.84±0.05 *(**)	1.44±0.06 **(*)	1.64±0.19 *(**)	1.90±0.21 **(**)	1.58±0.18 **(**)	1.14±0.07 **(**)	0.94±0.04 **(**)
PE6		0.86±0.03 (*)	1.39±0.11 **(**)	1.81±0.17 **(*)	1.73±0.21 **(**)	1.76±0.24 **(**)	1.12±0.12 **(**)	0.94±0.05 **(**)
PE7		0.84±0.04 *(**)	1.39±0.11 *(**)	1.56±0.14 **(**)	1.63±0.25 **(**)	1.31±0.07 **(**)	1.12±0.07 *(**)	0.92±0.03 **(**)
PE8		0.82±0.08 *(**)	1.02±0.07 **(**)	1.14±0.06 **(**)	1.33±0.13 **(**)	1.19±0.09 **(**)	1.01±0.04 **(**)	0.89±0.04 **(**)
PE9		0.87±0.04 *(*)	1.03±0.08 **(**)	1.13±0.07 **(**)	1.06±0.07 **(**)	0.98±0.05 **(**)	0.95±0.02 **(**)	0.89±0.02 **(**)
Control	10mg/kg	0.86±0.03	0.89 ±0.03	0.98±0.03	1.02±0.05	1.01±0.06	0.99±0.04	0.97±0.04
Aspirin		0.93±0.02	1.98±0.035	2.91±0.03	3.71±0.07	3.15±0.02	2.13±0.04	1.68±0.03

Table 2: Analgesic potential of compound PE1-PE9 at 30 mg/kg in comparison with control and standard

Comp.	Dose	Latency time (seconds)						
		0min	30 min	60 min	90 min	120 min	150 min	180 min
PE1	30mg/kg	0.87±0.06 *(**)	1.46±0.18 **(**)	1.86±0.25 **(**)	1.97±0.21 **(**)	2.28±0.11 **(**)	2.07±0.07 **(*)	1.28±0.13 **(*)
PE2		0.86±0.05 (**)	1.39±0.12 **(**)	2.23±0.15 **(*)	3.10±0.08 **(*)	2.60±0.23 **(*)	1.95±0.04 **(**)	1.15±0.08 **(**)
PE3		0.90±0.07(*)	1.27±0.14 **(**)	1.97±0.13 **(**)	2.46±0.06 **(**)	2.30±0.11 **(**)	1.92±0.06 **(**)	1.25±0.06 **(*)
PE4		0.84±0.04 *(**)	1.53±0.09 **(**)	2.03±0.29 **(*)	2.33±0.30 **(**)	1.97±0.29 **(**)	1.33±0.08 **(**)	1.15±0.12 **(**)
PE5		0.84±0.06 *(**)	1.93±0.11 **(*)	2.31±0.22 **(*)	2.35±0.29 **(**)	1.99±0.21 **(**)	1.49±0.14 **(**)	1.06±0.08 **(**)
PE6		0.84±0.04 *(**)	2.70±0.39 **(**)	2.33±0.47 **(*)	2.19±0.44 **(**)	1.88±0.32 **(**)	1.24±0.19 **(**)	1.02±0.09 **(**)
PE7		0.86±0.03 (**)	2.27±0.17 **(**)	2.40±0.48 **(*)	2.81±0.26 **(*)	2.15±0.31 **(**)	1.42±0.23 **(**)	1.04±0.06 **(**)
PE8		0.87±0.03 *(**)	1.48±0.17 **(**)	1.28±0.07 **(**)	1.81±0.20 **(**)	1.43±0.12 **(**)	1.20±0.06 **(**)	0.92±0.03 **(**)
PE9		0.87±0.04 *(**)	1.74±0.24 **(*)	1.95±0.24 **(**)	2.33±0.20 **(**)	2.17±0.14 **(**)	2.09±0.08 **(*)	1.25±0.06 **(*)
Control	10mg/kg	0.86±0.03	0.89±0.03	0.98±0.03	1.02±0.05	1.01±0.06	0.99±0.04	0.97±0.04
Aspirin		0.93±0.02	1.98±0.03	2.91±0.03	3.71±0.07	3.15±0.02	2.13±0.04	1.68±0.03

n=7 values are mean±2 SEM, *= p<0.05 significant difference as compared to control (10%DMSO)
**= p<0.01 highly significant difference as compared to control, (*)=p<0.05 significant difference as compared to standard (aspirin)
(**)=p<0.01 highly significant difference as compared to standard

(MeOH)nm: 206, 263; IRυ_{max} (KBr) cm^{-1}: 3439, 3096, 2917, 1596, 1443, 1031; EIMS m/z (%): 470.17 M^+ (32.4), 436(17.2), 393(52.4), 263(36), 275(12.5), 221(35.8), 207(68.2), 194(100); ^{1}H-NMR ($CDCl_3$, 500MHz) δ(ppm): 0.896-0.887 (d, *J*= 4.5 Hz, 4H, H-20), 2.534-2.527 (m, 3H, H-13b), 2.731-2.725 (m, 4H, H-11, 13a), 3.023-2.986 (m, 5H, H-9), 3.417-3.398 (m, 2H, H-10), 4.081-3.985 (m,4H, H-12), 7.026-6.987(d, *J*=19.5 Hz, H, H-18), 7.217-7.204 (m, 2H, H-15, 19), 7.354-7.347 (m, 9H, H-23, 24, 25, 26, 28, 29, 30, 31, 32, 5), 7.652-7.641 (d, *J*= 5.5Hz, 2H, H-22, 26), 9.571 (s, 2H, H-33, 34), 10.995 (s, 1H, H-6).

Analgesic activity

By using reported methodology and doses compounds were evaluated for analgesic activity (Akhter *et al*., 2019). The percent pain protection against thermal stimuli was calculated by applying following formula:

$$\text{Percent pain protection} = \frac{\text{Drug mean latency time} - \text{Control mean latency time}}{\text{Control mean latency time}} \times 100$$

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) version 21 SPSS and one-way ANOVA were applied for Statistical analysis, the significant difference value ($p<0.05$) and highly significant difference value ($p<0.01$) was indicated by * and ** for control groups while (*) and (**) for standard aspirin.

RESULTS

Percent yield of parent molecule was high enough (92%) so other derivatives from parent compound was easily synthesized. Analgesic potency of compounds was evaluated by tail flick method and presented in Tables 1-2 and in figs. 1-2.

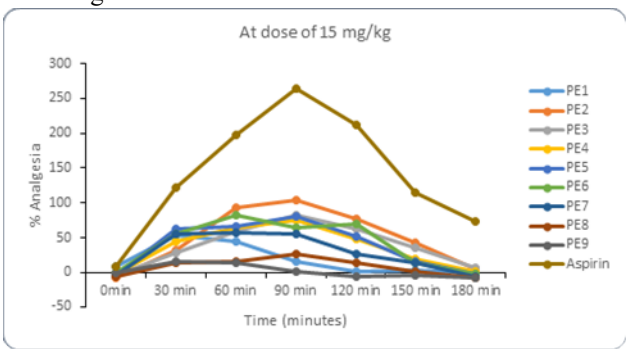


Fig. 1: Percent pain protection of compounds and standard at 15 mg/kg

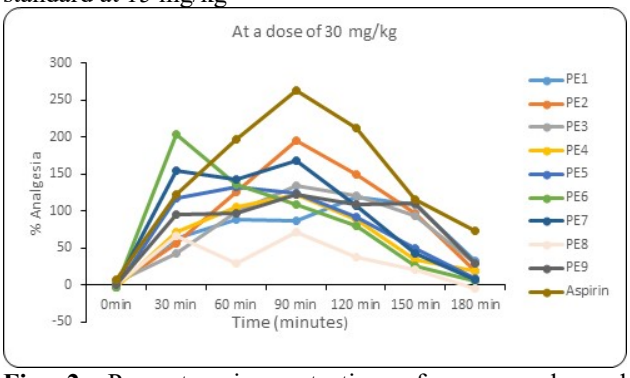


Fig. 2: Percent pain protection of compounds and standard at 30 mg/kg

DISCUSSION

Chemistry

All the synthesized derivatives were structurally verified through spectral studies including UV/visible, EIMS, FTIR and ^{1}HNMR. Compound PE5 was obtained as light greenish yellow amorphous powder having yield 75.5% and melting point is 210±04ºC. Molecular ion peak at m/z 483 was found through EIMS, fragmentation pattern confirmed the molecular formula of novel compound as $C_{27}H_{25}N_5O_2S$.The characteristics FTIR absorption band of different functional groups at 3439 for amine (-NH), at 1586 for thiazole (-NH) and at 619 for thiazole (C-S) also support the molecular formula. Ultra violet spectra showed maximum absorptions at 257nm and 295nm due to transition of pi electron in thiazole ring.

Proton integration curve in ^{1}HNMR spectra showed the presence of methyl group at 0.898ppm in the form of doublet, a multiplet at 7.542ppm confirmed the protons of three benzene rings, a singlet at 7.305ppm from thiazole ring and two axial and equatorial protons in the range of 2.421-2.684ppm confirmed the saturated carbon hydrogen bond in cyclic ring. From the above mention data of PE5, the compound was structurally confirmed as (Z)-2-(2-(3-methyl-2,6-diphenylpiperidin-4-ylidene) hydrazinyl)-4-(4-nitro phenyl) thiazole. Similarly, the structures of other compounds were elucidated.

Analgesic activity

Different class of analgesic agents have own associated toxicities. Opioid cause addiction, non-steroidal anti-inflammatory agents causes kidney damage and over use of acetaminophen result in liver damage. Currently the development of effective and safe analgesic agent is the goal of many research studies, in this context we evaluated the synthesized compound for analgesic activity.

Synthesized compounds showed varying degree of analgesic activity presented in tables 1 and 2. All the compounds showed dose dependent activity, latency time increases at high dose. Significant analgesia observed after 30 minutes of administration and gradually increases with time and maximize at 120-150 minutes at 30mg/kg. At 15mg/kg compound showed maximum analgesic effect after 90 minutes of administration. Thiosemicarbazone derivative (PE2) showed better activity when compared with piperidin-4-one (PE1) and thiazole derivatives (PE3-PE9). PE6 having bromo substitution is highly active as compared to control but not significant as compared to standard drug, exhibited potent analgesia with rapid onset of action, after 30 minutes of administration it showed maximum effect and then gradually decrease.

PE7 having methoxy substitution showed good analgesic activity, its onset of action is fast and persist for 120 minutes then fall down gradually up to 180 minutes. PE5 and PE4 containing nitro ($-NO_2$) substitution displayed similar to PE7 with less effectiveness. PE2 displayed onset of activity at 30 minutes and sustained till 180 minutes showed good analgesic potential throughout the experiment. Cyclization of thiosemicarbazide causes decreased in activity might be due to variation in the pharmacokinetics properties.

Results revealed that all the compounds have potency to reduce the pain, presence of piperidine functional group

along phenyl and thiazole ring make compounds effective against pain receptors.

By comparing the results of previously reported compounds (Siddiqui, Akhter *et al*., 2019) with current study we found that the analgesic potency is effected by the substitution at third position in the piperidin-4-one ring. 3,3- dimethyl substituted derivatives are more potent than 3-methyl substituted derivatives.

CONCLUSION

The present study provides a process for preparing piperidine based derivatives having analgesic activity. Starting from simple chemicals including aromatic aldehyde and aliphatic ketone an efficient three step process was utilized to developed complex hydrazinyl thiazole derivatives of piperidin-4-one with high yield (55-98%). All compounds showed ability to reduce pain of varying degree. Thiosemicarbazone derivative (PE2) displayed better activity as compared to other compounds. Current study is a continuation of our previous reported attempt to compare the structure activity relationship between compounds. Preliminary pharmacological testing showed that 3 methyl derivatives exhibited less analgesic activity than those having 3,3 dimethyl substitution on piperidin-4-one ring, might be more hydrophobic area available at binding site or it may affect the pharmacokinetics properties of compounds, a detail study is required to indorse these findings. These compounds can be further optimized to produce good analgesic agents in the future.

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