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**Original Article**

# Synthesis and pharmacological study of substituted amino-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamides

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## ABSTRACT

Ulcers are not usually life threatening, however they can cause serious damage which may leads to cancer if untreated. In the present study with the intension of enhancing the array of therapeutic ammonites to treat ulcer a series of thiazolidinone derivatives **(4a-4f)** were synthesized from substituted Schiff bases with thioglycolic acid in presence of anhydrous zinc chloride. The structures of these synthesized compounds have been characterized on the basis of physical constants, spectral data and evaluated them for their possible antiulcer activity using ethanol induced gastric lesion model. All the compounds studied showed significant antiulcer activity against ethanol induced gastric ulcers. Lansoprazole was used as a standard drug for comparison and the Compound **4f** protected animals from ethanol induced ulcers at the dose of 300 mg/kg, which is comparable to that of standard drug lansoprazole (300 mg/kg).

**KEY WORDS:** Thiazolidinone, Antiulcer activity, Ethanol induced gastric lesion model, Lansoprazole.

## INTRODUCTION

Thiazolidinones are the derivatives of thiazolidinebelongs to an important group of heterocyclic compounds [1]. Thiazolidinones with carbonyl group at 2nd, 4th or 5thposition have been subjected to extensive study in the recent past[2]. Numerous reports have appeared in the literature, which highlights their chemistry and uses[3]. It was observed from the literature that certain compounds bearing thiazolidinone nucleus have wide range of applications in medicinal chemistry[4] and hence thiazolidinones have been studied extensively due to their various biological activities however, there is a paucity of literature on their antiulcer activity. The treatment of ulcer is more challenging as it become worsens if untreated[5].

It was found in the literature that the currently used drugs for the treatment of ulcer are associated with side effects[6]. Hence there is a need for the synthesis of effective drugs which are devoid or minimum of side effects. In view of this in the present study an attempt was made to synthesize, characterize and evaluate the possible antiulcer activity of thiazolidinone derivatives.

## MATERIALS AND METHODS

The melting point of the synthesized compounds were determined in open capillary using LABHOSP melting point apparatus and recorded without correction. Progress of the reaction and the purity of the compounds were checked using precoated silica gel TLC plates (60 GF, 254 MERCK) and a mixture of n-hexane and ethyl acetate (4:1) as a mobile phase[7]. The IR spectra of the synthesized compound were recorded on SHIMADZU FTIR 8400 spectrometer by KBr pellet technique [8]. The $^1$HNMR Spectra of the synthesized compounds were taken using BRUKER SPECTROSPIN-400MHz spectrometer using methanol/acetone as solvent and TMS as internal standard [9]. The chemical shift datas were expressed as δ ppm.

### General procedure:

***Synthesis of substituted Ethyl(phenyl amino) acetates(1a-1f):*** Ethylchloroacetate (0.2mol, 21.3 ml) was refluxed with Aniline/substituted aniline(0.1mol) in dry acetone (25 ml) and anhydrous potassium carbonate (0.1 mol, 13.6 g) for 8 hr. The solvent was evaporated and the reaction mixture was poured into crushed ice. The

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solid thus separated was filtered, dried and recrystallized from petroleum ether. Reaction progress was monitored by TLC.

***1a: ethyl phenyl amino acetate:*** Yield:48.5%; m.p:53; Rf:0.78; IR(KBr $cm^{-1}$): 1604(C=O), 3385(NH), 1259(C-0-C), 1512(C-C Ar)

***1b: ethyl [(4-nitro phenyl) amino] acetate:*** Yield:47%; m.p:148; Rf:0.8; IR(KBr $cm^{-1}$): 1631(C=O), 3360(NH), 1201(C-0-C), 1475(C-C Ar), 1325(Ar $NO_2$).

***1c: ethyl [(4-chloro phenyl) amino] acetate:*** Yield:62%; m.p:60; Rf:0.7; IR(KBr $cm^{-1}$): 1630(C=O), 3375(NH), 1577(C-C Ar), 638(Ar Cl).

***1d: ethyl [(2-nitro phenyl) amino] acetate:*** Yield:67%; m.p:66; Rf:0.25; IR(KBr $cm^{-1}$): 1630(C=O), 3344(NH), 1471(C-C Ar), 1320(Ar $NO_2$).

***1e:ethyl [(4-methoxy phenyl) amino] acetate:*** Yield:72%; m.p:123; Rf:0.37; IR(KBr $cm^{-1}$): 1604(C=O), 3385(NH), 1465(C-C Ar), 1320(Ar $NO_2$).

***1f: ethyl [(3-nitro phenyl) amino] acetate:*** Yield:60%; m.p:123; Rf:0.42; IR(KBr $cm^{-1}$): 1604(C=O), 3385(NH), 1465(C-C Ar), 1320(Ar $NO_2$).

***Synthesisof substituted 2-(phenylamino) acetohydrazides (2a-2f):*** Substituted (ethyl phenyl amino) acetates *1a-1f*(0.01 mol) were refluxed on water bath with excess of hydrazine hydrate (0.02 mol, 0.9 ml) in ethanol (25 ml) for 10 hr. The solvent was evaporated and the product thus obtained were washed with cold water, dried and purified by recrystallization with methanol.The progresses of the reactions were monitored by TLC.

***2a: phenyl amino acetohydrazide:***Yield:42%; m.p:115; Rf:0.62; IR (KBr $cm^{-1}$): 3340, 3304($NH_2$), 3018(Ar CH), 1579(CN).

***2b: 2-[(4-nitro phenyl) amino]acetohydrazide:*** Yield:45%; m.p:128; Rf:0.69; IR (KBr $cm^{-1}$): 3240, 3219($NH_2$), 3107(Ar CH), 1587(CN), 1469(C-C Ar), 1550($ArNO_2$).

***2c: 2-[(4-chloro phenyl) amino] acetohydrazide:*** Yield:45%; m.p:72; Rf:0.27; IR (KBr $cm^{-1}$): 3471, 3381($NH_2$), 2980(Ar CH), 1589(CN), 1494(C-C Ar), 638(Ar Cl).

***2d: 2-[(2-nitro phenyl) amino] acetohydrazide:*** Yield:42%; m.p:60; Rf:0.4; IR (KBr $cm^{-1}$): 3475, 3348($NH_2$), 3174(Ar CH), 1344(CN), 1568(C-C Ar), 1550(Ar $NO_2$).

***2e: 2-[(4-methoxy phenyl) amino] acetohydrazide:*** Yield:72%; m.p:128; Rf:0.6; IR (KBr $cm^{-1}$): 3317, 3302($NH_2$), 3174(Ar CH), 1344(CN), 1427(C-C Ar), 1550(Ar $NO_2$).

***2f: 2-[(3-nitro phenyl) amino] acetohydrazide:*** Yield:68%; m.p:128; Rf:0.68; IR (KBr $cm^{-1}$): 3317, 3302($NH_2$), 3174(Ar CH), 1344(CN), 1427(C-C Ar), 1550(Ar $NO_2$).

***Synthesis of substituted N'-benzylidene-2-(phenylamino) acetohydrazides.(3a-3f):*** Each of the above substituted 2-(Phenyl amino) acetohydrazides (0.01mol) were added to substituted arylaldehydes (0.01 mol) and refluxed with few drops of glacial acetic acid in ethanol (25 ml) for 8 hrs. The solid thus obtained was filtered, washed with cold water, dried and recrystallized from methanol. Reaction progress was monitored by TLC.

***3a: $N^1$-benzylidene-2-(phenyl amino) aceto hydrazide:*** Yield:45%; m.p:125; Rf:0.82; IR (KBr $cm^{-1}$): 3045(Ar CH), 1660(CN), 1599(C-C Ar); $^1$HNMR(δppm): 7.14-7.65(m, 9H, ArH), 8.9(s, 1H, NCH).

***3b: $N^1$-benzylidene-2-[(4-nitro phenyl) amino] acetohydrazide:*** Yield:54%; m.p:122; Rf:0.85; IR (KBr $cm^{-1}$): 3107(Ar CH), 1629(CN), 1469(C-C Ar).

***3c: $N^1$-benzylidene-2-[(4-chlorophenyl) amino] acetohydrazide:*** Yield:71%; m.p:38; Rf:0.6; IR (KBr $cm^{-1}$): 3066(Ar CH), 1687(CN), 1600(C-C Ar).

***3d: $N^1$-benzylidene-2-[(2-nitro phenyl) amino] acetohydrazide:*** Yield:52%; m.p:162; Rf:0.3; IR (KBr $cm^{-1}$): 3050(Ar CH), 1595(CN), 1682(C-C Ar).

***3e: $N^1$-benzylidene-2-[(4-methoxyphenyl) amino]acetohydrazide:*** Yield:81%; m.p:36; Rf:0.4; IR (KBr $cm^{-1}$): 3045(Ar CH), 1660(CN), 1612(C-C Ar).

***3f: $N^1$-benzylidene-2-[(3-nitro phenyl) amino] acetohydrazide:*** Yield:54%; m.p:135; Rf:0.48; IR (KBr $cm^{-1}$): 3045(Ar CH), 1672(CN), 1612(C-C Ar), 1327((Ar-$NO_2$))

***Synthesis of substituted2-(phenylamino)-N'-[(Z)-phenylmethylidene]acetohydrazide derivatives(4a-4f):*** To an equimolar mixture of (0.01 mol)acetohydrazides*(3a-3f)*and thioglycholic acid (0.01mol , 0.7 ml) in 20ml of DMF, a catalytic amount of anhydrous $ZnCl_2$was added and the reaction mixture was refluxed for 8 hours, reaction progress was monitored by TLC. The solvents were recovered under reduced pressure and the respective residues thus resulted were dissolved in dichloromethane and washed with 10% sodium bicarbonate solution, dried over anhydrous sodium sulphate and the solvent was recovered under reduced pressure. The obtained residues were then recrystallized from ethanol **(scheme 1).**

***4a:N-[4-oxo-2-phenyl-1,3-thiazolidin-3-yl]-2-(phenylamino) acetamide:***Yield:68%;m.p:110; Rf:0.5; IR (KBR $cm^{-1}$): 1678 (C=O), 1226 (Ar-F), 1506 (C=C Ar); $^1$HNMR (δppm):3.38(s, 2H, S-$CH_2$), 3.9(d, 2H, NH-$CH_2$), 5.9(s, 1H, S-CH), 6.5-7.1(m, 10H,Ar-H), 8.0(s, 2H, NH).

***4b:2-[(4-nitrophenyl)amino]-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl) acetamide:*** Yield:65%;

m.p:121; Rf:0.26; IR (KBr $cm^{-1}$):1336 (C-N), 1687 (C=O), 1469 (C=C Ar),1504(N=O); $^1$HNMR(δppm): 3.38(s, 2H, S-$CH_2$), 5.9(s, 1H, S-CH), 6.5-7.1(m, 9H,Ar-H), 7.0(d, 2H, NH-$CH_2$), 8.0(s, 2H, NH).

***4c:2-[(4-chlorophenyl)amino]-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide:*** Yield:75%; m.p:133; Rf:0.34; IR (KBr $cm^{-1}$): 1330(C-N), 3024(CH stretch), 1446 (C=C Ar), 717 (CH- Ar), 1691 (C=O); $^1$HNMR(δppm): 3.53(s, 2H, S-$CH_2$), 4.84(s, 1H, S-CH), 7.0(d, 2H, NH-$CH_2$), 7.21-7.95(m, 9H,Ar-H).8.0(s, 2H, NH).

***4d:2-[(2-nitrophenyl)amino]-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide:*** Yield:52%; m.p:156; Rf:0.3; IR (KBr $cm^{-1}$): 1728(C=O), 1537($NO_2$), 1450(C=C Ar), 839(CH- Ar), 1047(C-N); $^1$HNMR(δppm):3.38(s, 2H, S-$CH_2$), 4.0(d, 2H, NH-$CH_2$), 5.9(s, 1H, S-CH), 6.5-7.1(m, 9H,Ar-H), 8.0(s, 2H, NH).

***4e:2-[(4-Methoxy phenyl)amino]-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide:*** Yield:52%; m.p:156; Rf:0.3; IR (KBr $cm^{-1}$): 1595(C=O), 3290(NH- str), 3057(CH stretch), 1390(CH bend), 1406(C=C Ar), 705(CH- Ar); $^1$HNMR(δppm): 3.38(s, 2H, S-$CH_2$), 5.9(s, 1H, S-CH), 6.5-7.1(m, 9H,Ar-H), 7.0(d, 2H, NH-$CH_2$), 8.0(s, 2H, NH).

***4f:2-[(3-nitrophenyl)amino]-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide:*** Yield:66%; m.p:150; Rf:0.5; IR (KBr $cm^{-1}$): 1693(C=O), 1346(CN), 3057(ArC-H stretch), 1390(C-H bend),$^1$HNMR(δppm): 3.53(s, 2H, S-$CH_2$), 4.826(s, 1H, S-CH), 7.31-7.38(m, 13H,Ar-H, NH-$CH_2$, NH).

## ANTIULCER ACTIVITY:

***Experimental animals:*** Healthy Wistar albino rats and swiss albino mice of either sex weighing between 100-200g and 20-30g respectively were used for the study and were procured from the animal house of the Drug testing laboratory, Bangalore. They were housed in well ventilated spacious animal house with 12±1h, day and night schedule in the animal house of our college under standard husbandry conditions and fed with a standard feed (Lipton India Limited, Bangalore) and water *adlibitum*. The experiments were conducted as per the guidelines of CPCSEA, Chennai, India(185/CPCSEA) and institutional ethical committee clearance(DCD/GCP/IAEC/02/2011-2012).

***Acute toxicity studies*[10]*:*** Acute toxicity studies were carried out on Swiss albino mice(20-30g). Fixed dose method of OECD guidelines No. 423 of CPCSEA was adopted for acute toxicity studies by the oral route at dose levels up to 2000 mg/kg of the synthesized compounds in 2% acacia suspension.

***Anti-ulcer activity*[11]:**Wistar albino rats of either sex weighing 100-200g were used for the study. The effects of the synthesized compounds were evaluated using ethanol induced ulcer model. Lansoprazole was used as a standard drug.

***Ethanol induced ulcer model*[11]*:*** Albino Wistar rats of either sex were divided into nine groups with six animals in each group as follows:

Group I: Normal Control (untreated) group.
Group II: Positive control group
Group III: Negative control group
Group IV: Standard(Lansoprazole 10 mg/kg)
Group V: compound 4b (300mg/kg)
GroupVI: Compound 4c (300mg/kg)
Group VII: Compound 4d (300mg/kg)
Group VIII: Compound 4e (300mg/kg)
Group IX: Compound 4f (300mg/kg)

Ulcers were induced by treating the animals with absolute alcohol at the dose of 1ml/300 g an hour before administration of the standard and the compounds on the day of experiments. The animals were sacrificed and the stomach was removed, opened along the greater curvature, lesions (fig.1-8) were examined with the help of hand lens (10X) and the scoring was calculated as follows.

0= Normal stomach
0.5=Red coloration
1.0=spot ulcers
1.5= haemorrhagic
2.0= ulcer greater than 3 but less than 5
3.0= ulcer greater than 5

The mean ulcer score for each animal was expressed as ulcer index and the percentage protection was calculated using the formula,

% Protection= $(100-U_t/U_c) *100$

Where,

$U_t$= ulcer index of the treated group
$U_c$= ulcer index of the control group.

## RESULTS AND DISCUSSION

The IR Spectra of the synthesized Schiff bases (3a–3f) showed the presence of C=N stretching bands at 1595-1699 $cm^{-1}$ which corresponded to imine or Schiff bases. In $^1$HNMR spectra of the synthesized compounds, singlet peak appeared around 8.5 δppm for imine protons, whereas the IR spectra of the synthesized thiazolidinones (4a-4f) showed the presence of C=O stretching bands at 1672-1728 $cm^{-1}$ corresponds to carbonyl group of the thiazolidinone ring. In $^1$HNMR spectra of the synthesized compounds prominent singlet peaks were observed at 3.38-3.53(2H, S-$CH_2$) and 4.896-5.9(1H, S-CH) δ ppm corresponds to the thiazolidinone protons. Compound 4f (300mg/kg, p.o) showed significant antiulcer activity, compared to the positive control group (ulcer induced group). Standard drug Lansoprazole (300mg/kg) was used as reference which showed significant decrease ulcer compared to the positive

control group Fig (1-8) Among the synthesized compounds, compound 4f is with electron withdrawing group $NO_2$ at meta position of phenyl ring attached to1,4-thiazolidinone showed ulcer protective activity of 72.75%. Compound 4c with electron withdrawing group –Cl at para position of aniline had showed ulcer protective activity 62.89%. Compound 4d with electron withdrawing group $–NO_2$ at ortho position of aniline had showed ulcer protective activity 64.25% and the compound 4e with electron releasing group $–OCH_3$ at para position of aniline exhibited ulcer protective activity of 64.84% where as compound 4b having electron withdrawing $NO_2$ group at para position of aniline with 58.98%**(Table1).**Since there is no significant alterations in the antiulcer potency of the compounds 4b-4e; it may be concluded that, alterations in the electron density at para and ortho positions of aniline nucleus is not having any vital role in determining the potency of compound. However, the present study needs further preclinical investigations in order to monitor toxic effects of the compounds.

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**Fig 1 : Normal rat stomach**


**Fig 2: Ethanol induced rat stomach**


**Fig 3: Lansoprazole treated rat stomach**

**Fig 4: Rat stomach treated with compound 4b**

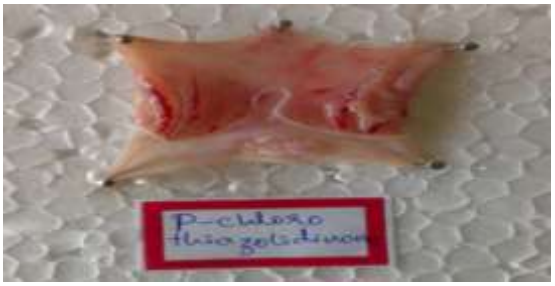


**Fig 5: Rat stomach treated with compound 4c**

**Fig 6: Rat stomach treated with compound 4d**

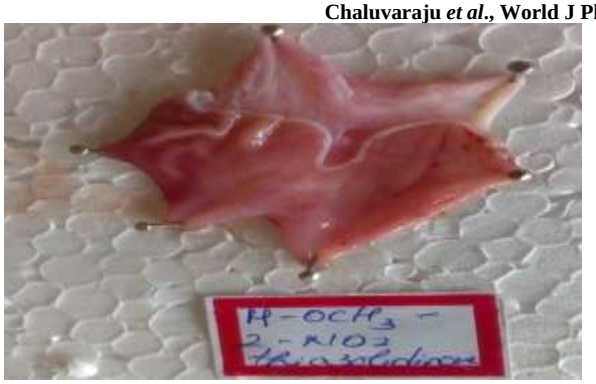
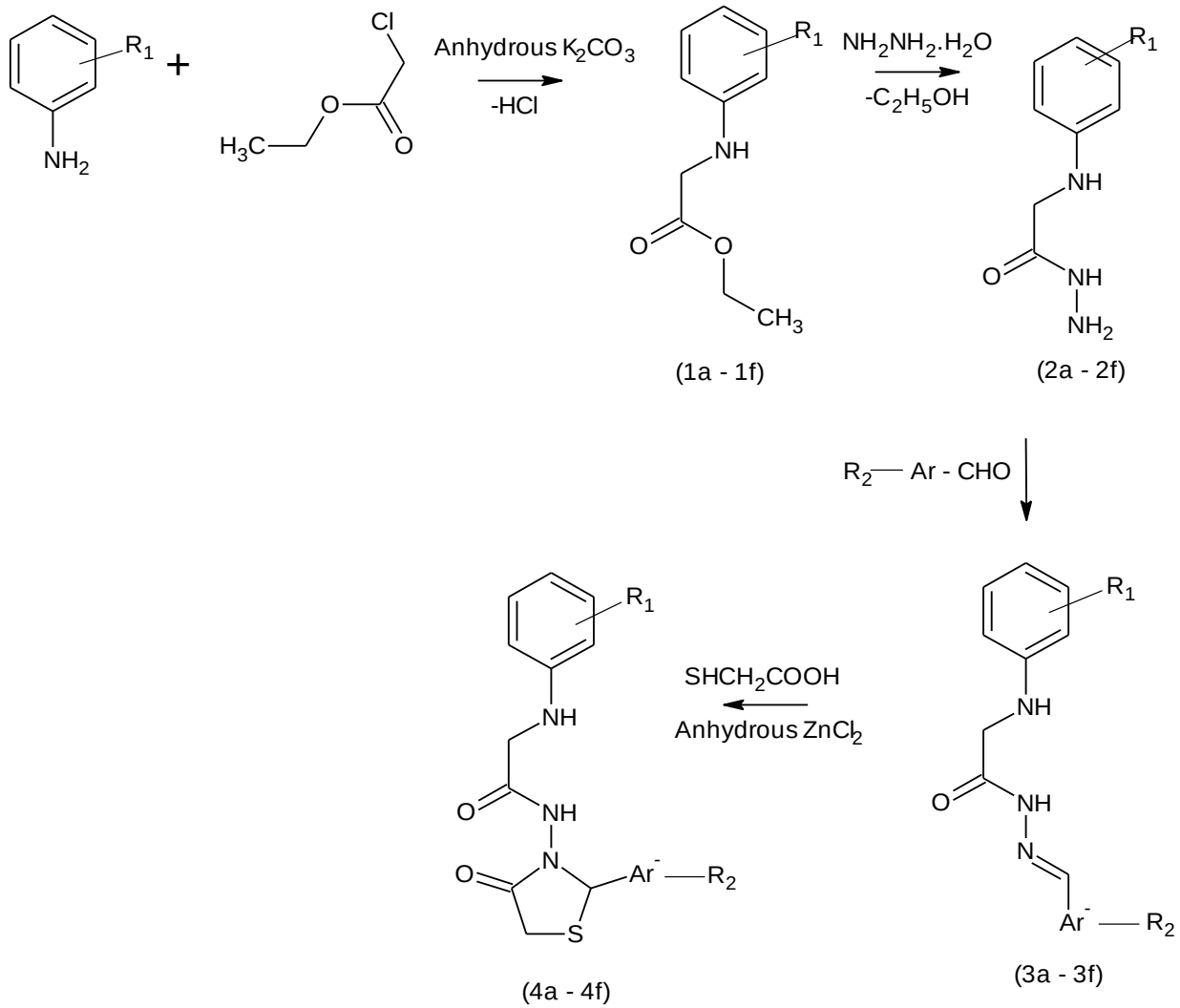


**Fig 7: Rat stomach treated with compound 4e**

**Fig 8: Rat stomach treated with compound 4f**

**Scheme I :**Synthetic protocol of substituted amino-n-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamides



Where,

| COMPOUND | $R_1$ | $R_2$ |
|---|---|---|
| 4a | H | H |
| 4b | 4-$NO_2$ | H |
| 4c | 4-Cl | H |
| 4d | 2-$NO_2$ | H |
| 4e | 4-0$CH_3$ | H |
| 4f | H | 3-$NO_2$ |

**Table I : Ulcer index and the percentage protection of Compound 4b-4f**

| **Treatment** | **Dose (mg/kg)** | **Mean Ulcer Index ±SEM** | **%age Protection** |
|---|---|---|---|
| Positive control(Ethanol) | - | 5.120±0.09661 | - |
| Standard (Lansoprozole) | 300 | ***1.350±0.03396 | 73.63 |
| Compound 4b | 300 | ***2.100±0.07519 | 58.98 |
| Compound 4c | 300 | ***1.900±0.04227 | 62.89 |
| Compound 4d | 300 | ***1.830±0.03235 | 64.25 |
| Compound 4e | 300 | ***1.800±0.08944 | 64.84 |
| Compound 4f | 300 | ***1.395±0.02012 | 72.75 |

Each value is expressed as mean ± SEM .
One-way ANOVA followed by Tukey's multiple comparison tests.

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