Tetrahedron Letters 53 (2012) 2897–2903

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Polyethylene glycol (PEG-400): an efficient and recyclable reaction medium for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives

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ARTICLE INFO

Article history:
Received 13 February 2012
Revised 30 March 2012
Accepted 31 March 2012
Available online 5 April 2012

Keywords:
PEG-400
Pyrazolo[3,4-*b*]quinoline
Aldehydes
Amino pyrazole
1,3-Cyclohexanedione
Recyclability

ABSTRACT

A simple, efficient, and eco-friendly synthetic protocol has been developed via one pot three-component reaction between aldehyde, amino pyrazole, and 1,3-cyclohexanedione by using recyclable polyethylene glycol (PEG)-400 as a reaction medium. Utilizing this protocol a variety of pyrazolo[3,4-*b*]quinoline derivatives were synthesized in excellent yields.

In recent years, scientists have started exploring environmentally benign synthetic organic transformations. The green chemistry has attracted the attention of the academia as well as industry.[1] Research for finding other alternate reaction media, which can substitute the hazardous, toxic, and inflammable organic solvents, which pose a serious threat to the environment, is gaining progress.[2] Many environmentally compatible reaction media like fluorous phases,[3] supercritical fluids,[4] and ionic liquids[5] are being used for several organic reactions. Each has its own advantages and is dependent on external factors like lipophilicity, pressure, and viscosity.

Over the years, polyethylene glycol (PEG) and modified polyethylene glycol derivatives have become more popular alternate reaction media, due to their interesting properties like non-toxicity, bio-compatibility, and bio-degradability when compared to other 'neoteric solvents' such as ionic liquids, super-critical fluids, and micellar systems.[6] PEG is a polymerized compound of ethylene oxide, which is hydrophilic in nature. It has benign characteristic properties with respect to environment and chemical industry such as low cost, reduced flammability, reduced toxicity, recyclability, facile degradability, and miscibility with various organic solvents likes toluene, dichloromethane, alcohol, and acetone.[7] Several organic transformations like substitution reactions,[8] oxidation and reduction reactions,[9] Heck reaction,[10] asymmetric dihydroxylation,[11] Suzuki cross-coupling reaction,[12] Wacker reaction,[13] and partial reductions of alkynes[14] were reported, using PEG as a recyclable medium.

Pyrazolo[3,4-*b*]quinoline derivatives are significant for their pharmacological activities. In particular, they exhibited potential antiviral,[15] antimalarial,[16] and antiinflammatory properties. These are also known for parasiticidic properties,[17] antibacterial, antitumor, hypotensive, and vasodilation activities.[18] Pyrazolo-annelated heterocyclic frame is the core moiety in numerous biologically active compounds, such as Celebrex, Analginum, Viagra, BAY 41-2272, and WYE-354 (Fig. 1) etc.[19]

Friedlander prepared pyrazolo[3,4-*b*]quinoline by the condensation of *o*-amino benzaldehyde with suitable pyrazoline-5-one.[20] This reaction affords several by-products along with pyrazoloquinoline. To overcome shortcomings, several methods are reported for the synthesis of pyrazolo[3,4-*b*]quinolines.[21] Recently Shi and Yang synthesized pyrazoloquinolines by using ionic liquid,[22] and Chebanov co-workers prepared these derivatives in the presence of microwave irradiation.[23] However, these reported protocols suffer from one or more drawbacks such as use of expensive reagents, harsh reaction conditions, prolonged reaction times, cumbersome product isolation procedures and low yields. Exploring a mild, efficient, and environmentally benign protocol for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives is highly desirable.

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http://dx.doi.org/10.1016/j.tetlet.2012.03.135

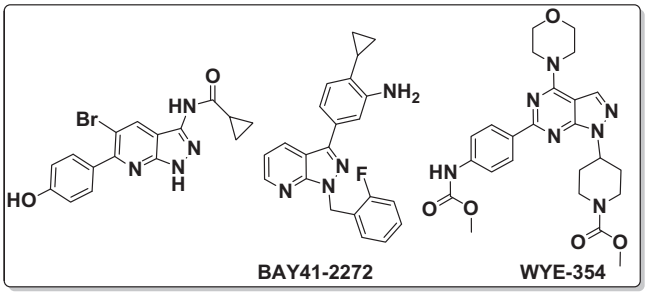
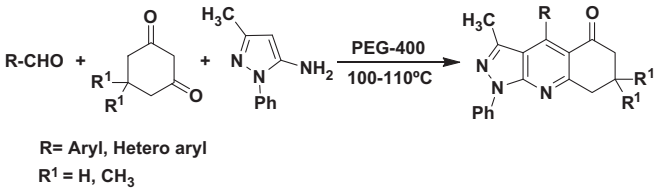


Figure 1. Biologically active pyrazolo[3,4-*b*]quinolines.



Scheme 1. Synthesis of pyrazolo[3,4-*b*]quinolines using PEG-400.

In continuation of our research toward the development of novel heterocyclic compounds,[24] employing environmentally benign reaction medium, herein we envisaged a simple and efficient one-pot three-component protocol for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives in moderate to high yields, using environment friendly polyethyelene glycol (PEG) as a recyclable reaction medium (Scheme 1). Initially, a model reaction was conducted by taking 4-methoxy benzaldehyde (1.0 mmol), 1,3-cyclohexanedione (1.0 mmol), and 5-amino-3-methyl-1-phenyl-pyrazole (1.0 mmol) at a temperature of 50–60 °C and the desired product was obtained in 36% yield only along with the unreacted starting materials, even after prolonged reaction time (24 h). This result prompted us to explore the ideal reaction condition to get maximum product yield. The reaction temperature was increased to 80–90 °C affording a better yield (74%). During further optimization study it was observed that 100–110 °C as the ideal temperature for the reaction and beyond 130 °C the reaction resulted in undesired side products. After optimizing the experimental conditions, 3,4,5-trimethoxy benzaldehyde (1.0 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), and 5-amino-3-methyl-1-phenyl-pyrazole (1.0 mmol) were reacted in the presence of recyclable polyethylene glycol (PEG)-400, resulting in the formation of the desired pyrazolo[3,4-*b*]quinoline derivative

Table 1
Synthesis of pyrazolo[3,4-*b*]quinoline derivatives by using PEG-400[a]

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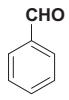
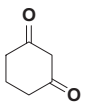
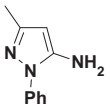
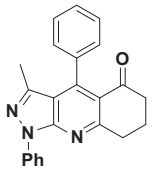
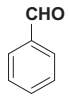
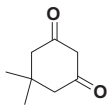
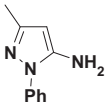
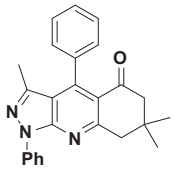
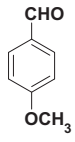
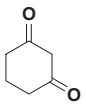
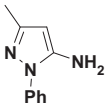
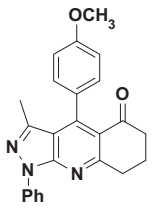
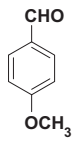
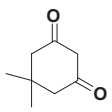
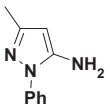
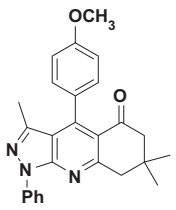
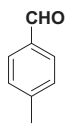
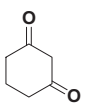
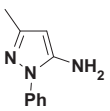
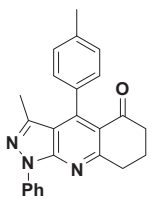
1					4	86
2					4	87
3					4	87
4					4	90
5					4	89

Table 1 (*continued*)

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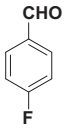
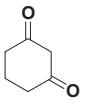
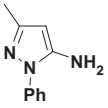
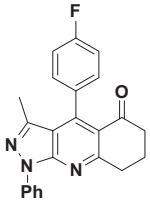
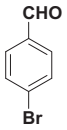
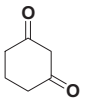
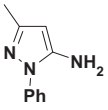
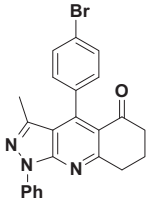
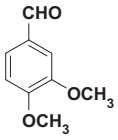
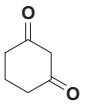
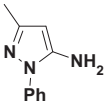
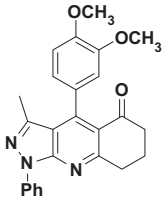
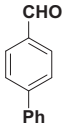
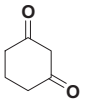
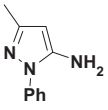
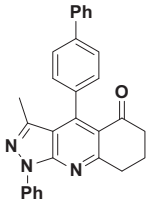
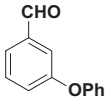
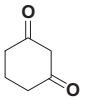
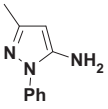
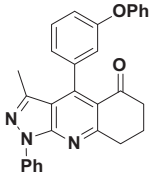
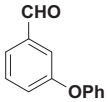
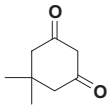
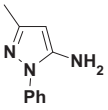
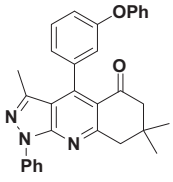
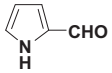
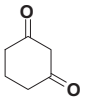
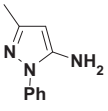
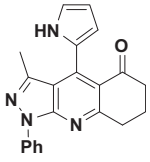
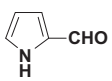
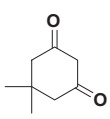
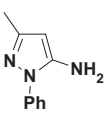
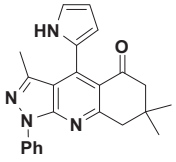
6					4	88
7					4	85
8					4	87
9					4	89
10					4	84
11					4	85
12					4	83
13					4	84

(*continued on next page*)

Table 1 (*continued*)

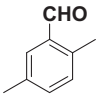
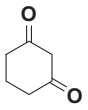
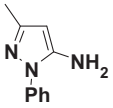
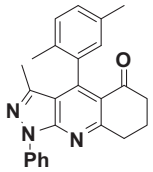
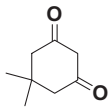
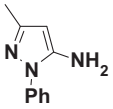
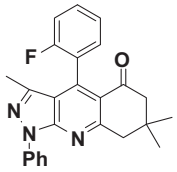
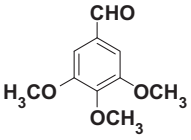
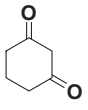
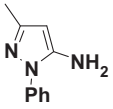
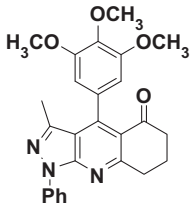
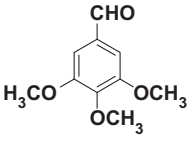
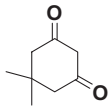
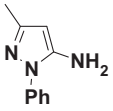
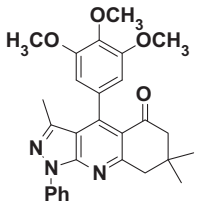
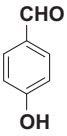
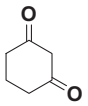
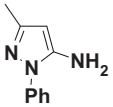
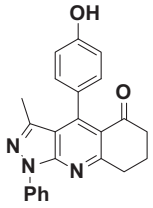
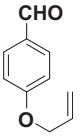
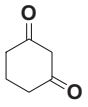
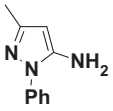
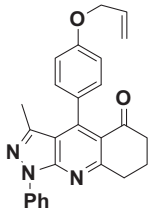
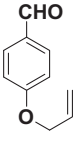
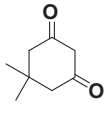
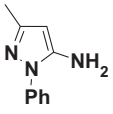
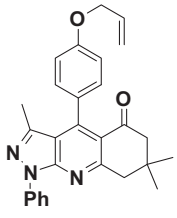
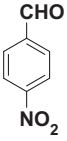
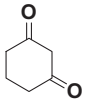
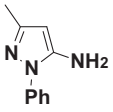
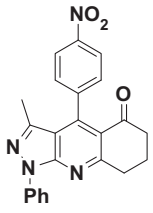
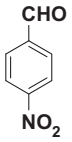
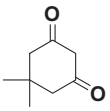
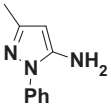
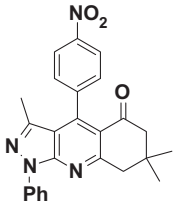
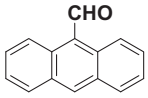
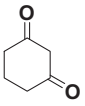
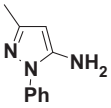
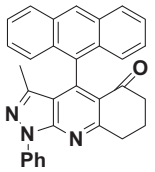
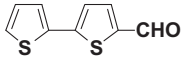
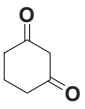
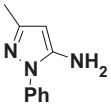
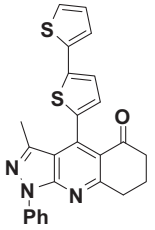
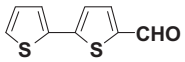
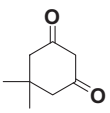
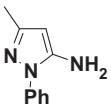
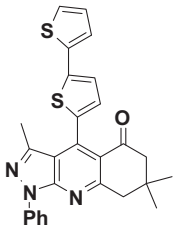
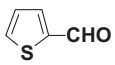
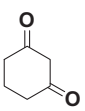
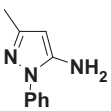
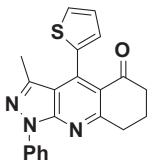
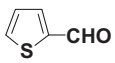
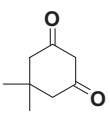
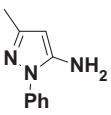
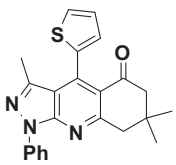
S. No.	Aldehyde	1,3-Dione	Pyrazolo amine	Product	Time (h)	Yield[b] (%)
14					4	85
15					4	83
16					4	90
17					4	92
18					4	91
19					4	86
20					4	88
21					4	75

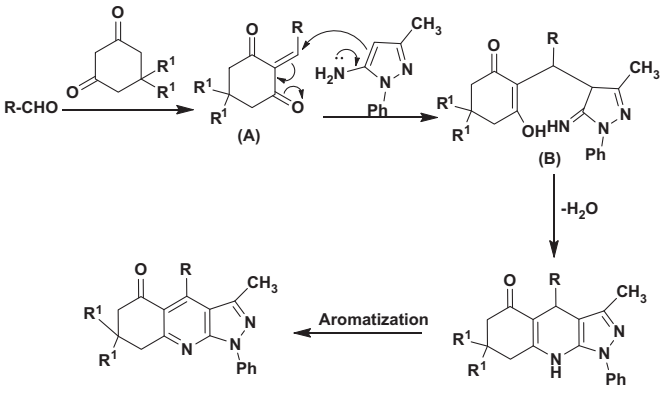
Table 1 (*continued*)

S. No.	Aldehyde	1,3-Dione	Pyrazolo amine	Product	Time (h)	Yield[b] (%)
22					4	76
23					4	80
24					4	82
25					4	84
26					4	82
27					4	83

[a] Reaction conditions: aldehyde (1.0 mmol), 1,3-cyclohexanedione (1.0 mmol), amino pyrazole (1.0 mmol), and PEG-400 at 110 °C.
[b] Isolated yields.

in excellent yield (Table 1, entry 17). The scope of this protocol was extended by reacting a variety of substituted aldehydes, resulting in a range of diversely substituted pyrazolo[3,4-*b*]quinoline derivatives. Aromatic aldehydes carrying either electron donating (Table 1, entries 3–5, 8, 16–18) or electron withdrawing (Table 1, entries 21 and 22) substituents reacted very well, affording moderate to high yields of pyrazoloquinoline derivatives (Table 1). Acid-sensitive aldehyde such as 2-thiophenecarboxaldehyde also reacted well and gave the corresponding pyrazoloquinoline derivative in satisfactory yields (Table 1, entry 26 and 27). Reaction was also conducted with bulky aromatic aldehydes having biphenyl, anthracene, and bithiophene groups (Table 1, entry 9, 23–25). Hetero aromatic aldehydes containing thiophene, pyrrole, and bithiophene also provided good yields (Table 1, entry 12 and 13, 24–27). Aldehydes with the substituents of phenoxy and allyloxy groups also transformed into the expected products (Table 1, entry 10 and 11, 19 and 20). Slightly diminished yields were obtained when nitro benzaldehyde was reacted (Table 1, entry 21 and 22). Scope of the reaction was also extended by reacting 1,3-cyclohexanedione as well as 5,5-dimethyl-1,3-cyclohexanedione.

The possible mechanism is described in Scheme 2. Initially, Knoevenagel condensation occurs between aldehyde and 1,3-cyclohexanedione, resulting in the adduct (A), which upon nucleophilic attack by amino pyrazole produces the Michael



Scheme 2. Possible mechanism.

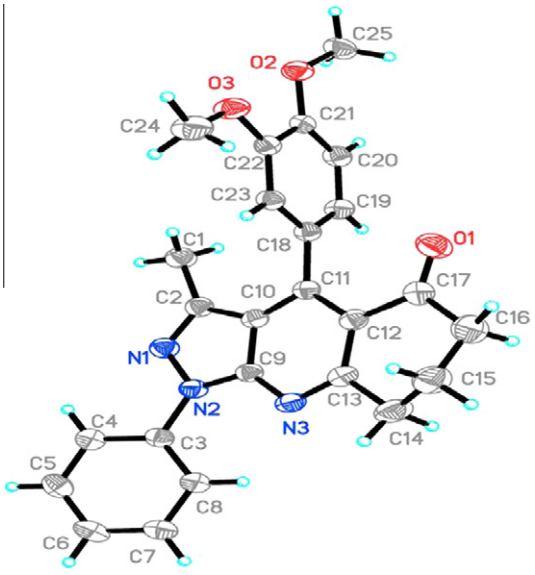


Figure 2. ORTEP diagram of compound **8** (30% probability).

adduct, as an intermediate (B). This intermediate on further cyclization, dehydration, and aromatization yields the final product as reported in the literature[25] and it was further supported by X-ray crystallography[26] (Fig. 2). All products were characterized by spectroscopic and analytical methods.[27,28]

In conclusion, we have demonstrated a mild and highly efficient protocol for the synthesis of pyrazolo[3,4-*b*]quinoline derivatives in excellent yields by using recyclable polyethylene glycol (PEG)-400 as a reaction medium. Environmental acceptability, economic viability, high yields, easy work-up, cleaner reaction profiles, and recyclability of PEG are the important features of this protocol.

Acknowledgments

We thank the CSIR, New Delhi, India, for fellowships to K.K., S.N.M., G.S. and the UGC for fellowship to K.R.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.135.

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26. X-ray data for the compound (Table 1, entry 8) was collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 5040 reflections in the range of 2.41 < θ < 27.86° for AM42. Integration and scaling of intensity data were accomplished using SAINT program. The structure was solved by direct methods using SHELXS97 and refinement was carried out by full-matrix least-squares technique using SHELXL97. Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C–H distances in the range of 0.93–0.97 Å and U_{iso}(H) values of 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for all other H atoms. Crystal data for AM42: $C_{25}H_{23}N_3O_3$, M = 413.46, Monoclinic, space group $P2_1/c$, a = 16.1526(12) Å, b = 8.4512(6) Å, c = 19.2357(10) Å, β = 125.526(4)°, V = 2137.0(2) Å^3, Z = 4, D_{calc} = 1.285 g/cm^3, T = 294(2) K, μ = 0.086 mm^{-1}, F(000) = 872, Mo Kα radiation, λ = 0.71073 Å, 19,783 reflections collected, 3749 unique (R_{int} = 0.0182), 3312 with $I > 2\sigma(I)$, R_1 = 0.0390, wR_2 = 0.1122, Final *GooF* = 1.035. Intensity data were measured on Bruker Smart Apex with CCD

area detector. CCDC 866149 contains supplementary crystallographic data for the structure. The crystallographic data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

27. *General procedure for the synthesis of Pyrazolo[3,4-b]quinoline derivatives*: To a stirred solution of polyethylene glycol (PEG)-400 (5 mL), aldehyde (1.0 mmol), 1,3-cyclohexadione (1.0 mmol) and amino pyrazole (1.0 mmol) were added and stirred at 100–110 °C, until the reaction was complete as indicated by TLC. After completion of the reaction as indicated by TLC, ether (5 mL) was added and stirred for a while and cooled to −50 °C. At this temperature the PEG became solid and the ether layer saturated with product was separated and evaporated. The crude product was recrystallized in ethanol to get analytically pure products in excellent yields. The recovered PEG was reused for further cycles.
28. *4-(4-Methoxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]-quinolin-5(6H)-one* (Table 1, *entry 4*): White crystals, mp 295–297 °C. IR (KBr) 3243, 3111, 2930, 1709, 1649, 1223, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ = 8.26 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 3.22 (s, 2H), 2.51 (s, 2H), 1.95 (s, 3H), 1.14 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 197.3, 163.4, 159.1, 150.3, 148.6, 145.5, 139.0, 129.2, 128.8, 128.4, 125.7, 120.9, 116.3, 113.3, 55.1, 54.0, 48.4, 32.1, 28.1, 14.4 ppm. ESI–MS: 412 $(M+H)^+$; $C_{26}H_{26}N_3O_2$. *3,7,7-Trimethyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-7,8-dihydro-1H-pyrazolo [3,4-b]quinolin-5(6H)-one* (Table 1, *entry 17*): White crystals, mp 316–319 °C. IR (KBr) 3241, 3113, 2924, 1709, 1652, 1227, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ = 8.24 (d, *J* = 8.3 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.44 (s, 2H), 3.94 (s, 3H), 3.84 (s, 6H), 3.24 (s, 2H), 2.55 (s, 2H), 1.99 (s, 3H), 1.15 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6, TMS) δ 197.1, 163.5, 152.9, 150.3, 148.4, 145.5, 138.9, 137.4, 132.8, 128.9, 125.9, 121.0, 119.8, 116.1, 104.5, 61.0, 56.0, 54.0, 48.5, 32.3, 28.1, 14.1 ppm. ESI–MS: 472 $(M+H)^+$; $C_{28}H_{30}N_3O_4$.